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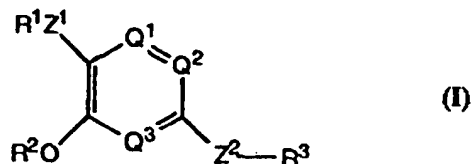
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(54) Title: SUBSTITUTED AROMATIC COMPOUNDS AS c.AMP PHOSPHODIESTERASE- AND TNF-INHIBITORS

(57) Abstract

This invention is directed to compounds of formula (I), wherein R¹ is an optionally substituted lower alkyl group; R² is an optionally substituted oxaliphatic group; R³ is an optionally substituted aryl group or an optionally substituted heteroaryl group; Q¹, Q² and Q³ are independently nitrogen, CX or CH; Z¹ is oxygen or sulfur; Z² is -CH=CH-, -C≡C-, -CH₂-CZ-, -CZCH₂-, -CZ-CZ-, -CH₂-NH-, -CH₂-O-, -CH₂-S-, -CX₂-O-, -CZNH-, -NH-CH₂-, -O-CH₂-, -SCH₂-, -SOCH₂-, -SO₂CH₂-, -O-CX₂-, -O-CZ-, -NH-CZ-, -N=N-, -NH-SO₂-, -SO₂-NH-, -CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH- or -NH-CO-NH-; Z is oxygen or sulfur; and X is halo; or an N-oxide thereof or a pharmaceutically acceptable salt thereof, which possess useful pharmaceutical properties. They are especially useful for inhibiting the production or physiological effects of TNF and inhibit cyclic AMP. The present invention is also directed to their pharmaceutical use, pharmaceutical compositions containing the compounds, and methods for their preparation.



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SUBSTITUTED AROMATIC COMPOUNDS AS c.AMP PHOSPHODIESTERASE- AND TNF-INHIBITORS

Field of the Invention

This invention is directed to substituted aromatic compounds, their preparation, pharmaceutical compositions containing these compounds, and
5 their pharmaceutical use in the treatment of disease states associated with proteins that mediate cellular activity.

Disease states associated with abnormally high physiological levels of cytokines such as TNF are treatable according to the invention. TNF is an important pro-inflammatory cytokine which causes hemorrhagic necrosis of
10 tumors and possesses other important biological activities. TNF is released by activated macrophages, activated T-lymphocytes, natural killer cells, mast cells and basophils, fibroblasts, endothelial cells and brain astrocytes among other cells.

The principal in vivo actions of TNF can be broadly classified as
15 inflammatory and catabolic. It has been implicated as a mediator of endotoxic shock, inflammation of joints and of the airways, immune deficiency states, allograft rejection, and in the cachexia associated with malignant disease and some parasitic infections. In view of the association of high serum levels of TNF with poor prognosis in sepsis, graft versus host disease and acute
20 respiratory distress syndrome, and its role in many other immunologic processes, this factor is regarded as an important mediator of general inflammation.

TNF primes or activates neutrophils, eosinophils, fibroblasts and
25 endothelial cells to release tissue damaging mediators. TNF also activates monocytes, macrophages and T-lymphocytes to cause the production of colony stimulating factors and other pro-inflammatory cytokines such as IL₁, IL₆, IL₈ and GM-CSF, which in some cases mediate the end effects of TNF. The ability of TNF to activate T-lymphocytes, monocytes, macrophages and related cells has been implicated in the progression of Human Immunodeficiency Virus (HIV)
30 infection. In order for these cells to become infected with HIV and for HIV replication to take place, the cells must be maintained in an activated state. Cytokines such as TNF have been shown to activate HIV replication in monocytes and macrophages. Features of endotoxic shock such as fever, metabolic acidosis, hypotension and intravascular coagulation are thought to
35 be mediated through the actions of TNF on the hypothalamus and in reducing the anti-coagulant activity of vascular endothelial cells. The cachexia associated with certain disease states is mediated through indirect effects on

protein catabolism. TNF also promotes bone resorption and acute phase protein synthesis.

The discussion herein relates to disease states associated with TNF and includes those disease states related to the production of TNF itself, and
5 disease states associated with other cytokines, such as but not limited to IL-1, or IL-6, that are modulated by associated with TNF. For example, a IL-1 associated disease state, where IL-1 production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state associated with TNF. TNF- α and TNF- β are also herein referred to collectively
10 as "TNF" unless specifically delineated otherwise, since there is a close structural homology between TNF- α (cachectin) and TNF- β (lymphotoxin) and each of them has a capacity to induce similar biologic responses and bind to the same cellular receptor.

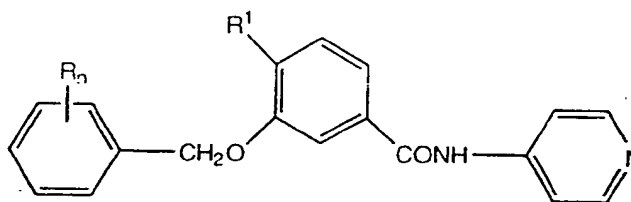
Disease states associated with pathological conditions that are
15 modulated by inhibiting enzymes, which are associated with secondary cellular messengers, such as cyclic AMP phosphodiesterase are also treatable according to the invention. Cyclic AMP phosphodiesterase is an important enzyme which regulates cyclic AMP levels and in turn thereby regulates other important biological reactions. The ability to regulate cyclic AMP
20 phosphodiesterase, including type IV cyclic AMP phosphodiesterase, therefore, has been implicated as being capable of treating assorted biological conditions.

In particular, inhibitors of type IV cyclic AMP phosphodiesterase have been implicated as being bronchodilators and asthma-prophylactic agents and
25 as agents for inhibiting eosinophil accumulation and of the function of eosinophils, and for treating other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. Inhibitors of cyclic AMP phosphodiesterase are also implicated in treating inflammatory diseases, proliferative skin diseases and conditions associated with cerebral
30 metabolic inhibition.

Reported Developments

Chemical Abstracts, 108(15), April 11, 1988, abstract no. 131583p pertains to an abstract of Japanese Patent Application Publication No. JP-A-62
35 158,253 which discloses that a substituted phenyl compound of formula

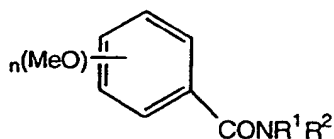
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is a cardiotonic, but does not disclose or suggest that the compound inhibits cyclic AMP phosphodiesterase or TNF. JP-A-62 158,253 also does not
 5 disclose or suggest that the moiety that is ortho to R¹ may be anything other than benzyloxy.

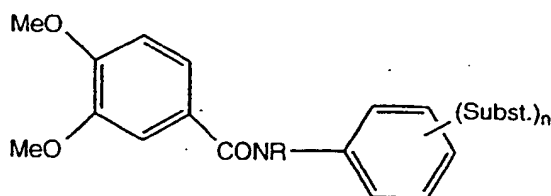
Chemical Abstracts, 99(6), August 8, 1983, abstract no. 43556z pertains to an abstract of Japanese Patent Application Publication No. JP-A-5 869,812 which discloses that a phenyl compound of formula

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is a hypoglycemic agent, but does not disclose or suggest that the compound inhibits cyclic AMP phosphodiesterase or TNF. JP-A-5 869,812 also does not
 15 disclose or suggest that the benzamide moiety may be substituted by anything other than methoxy.

Panos Grammaticakis, Bull. Soc. Chim. Fr., 848-857 (1965) discloses a phenyl compound of the formula

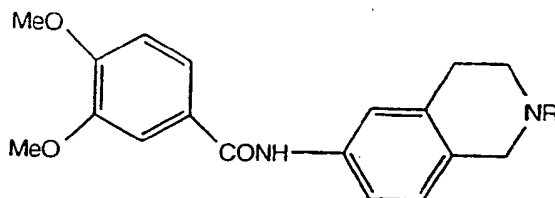


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Grammaticakis examines the ultraviolet and visible absorbances of compounds bearing different substituents. Grammaticakis does not disclose or suggest that the compound exhibits any pharmacological activity.

25 Ian W. Mathison, et al., J. Med. Chem., 16(4), 332-336 (1973), discloses that a phenyl compound of formula

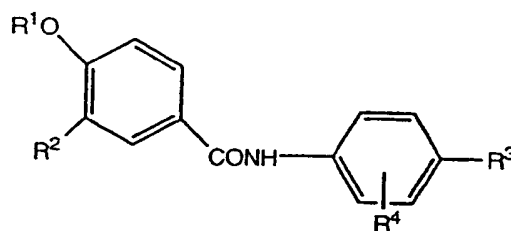
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is a hypotensive agent, but do not disclose or suggest that the compound
 5 inhibits cyclic AMP phosphodiesterase or TNF. Mathison, et al., also do not
 disclose or suggest that the benzamide moiety may be substituted by anything
 other than methoxy.

European Patent Application Publication No. EP 232199 B1 discloses
 that phenyl compounds of formula

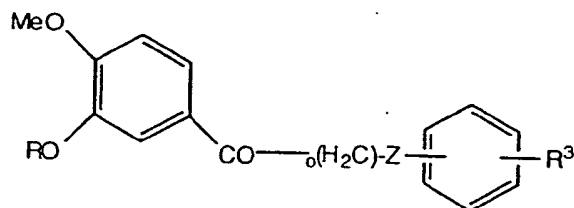
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wherein R^2 is alkyl or mono- or polycyclic cycloalkyl, exhibit anti-inflammatory
 and/or anti-allergic activity. EP 232199 B1 does not disclose or suggest
 15 compounds wherein the R^2 substituent is bonded to the phenyl moiety via an
 oxygen or sulfur atom.

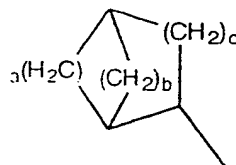
European Patent Application Publication No. EP 470,805 A1 discloses
 phenyl compounds of the formula

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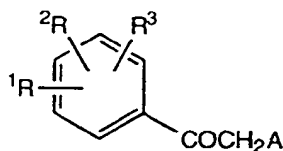
wherein R may be C₃₋₇ alkyl, C₃₋₇ cycloalkyl or

- 5 -



Z may be a bond; o is 1-4; a and b are independently 1-3; and c is 0-2. EP 470,805 A1 discloses that these compounds are useful intermediates for preparing PDE IV inhibitors, but does not disclose or suggest that the compounds have any pharmacological activity.

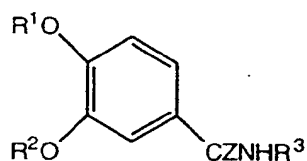
Japanese Patent Application Publication No. JP-A-0 4360847 discloses compounds of the formula



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wherein R¹, R² and R³ may be the same or different and may be optionally substituted lower alkyl(O); and A may be optionally substituted aryl or 5-6 membered heterocyclyl group. JP-A-0 4360847 discloses that the compounds are useful intermediates for preparing antimicrobial agents, but does not disclose or suggest that the compounds have any pharmacological activity.

WO Patent Application No. 92/12961 discloses that compounds of the formula



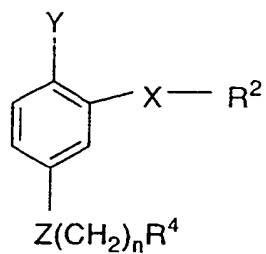
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inhibit cyclic AMP phosphodiesterase. WO Patent Application No. 92/12961 does not disclose or suggest that these compound inhibit TNF. WO Patent Application No. 92/12961 also does not disclose compounds wherein R² is an oxaaliphatic moiety.

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WO Patent Application No. 93/25517 discloses that compounds of the following formula inhibit PDE IV. WO Patent Application No. 93/25517 does

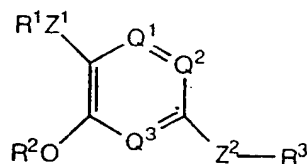
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not disclose or suggest that these compound inhibit TNF. WO Patent
Application No. 93/25517 also does not disclose compounds wherein R² is an
5 oxaaliphatic moiety.

SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I:-



5

wherein

R¹ is an optionally substituted lower alkyl group;

R² is an optionally substituted oxaaliphatic group;

R³ is an optionally substituted aryl group or an optionally substituted

10 heteroaryl group;

Q¹, Q² and Q³ are independently nitrogen, CX or CH;

Z¹ is oxygen or sulfur;

Z² is -CH=CH-, -C≡C-, -CH₂-CZ-, -CZCH₂-, -CZ-CZ-, -CH₂-NH-,

-CH₂-O-, -CH₂-S-, -CX₂-O-, -CZNH-, -NH-CH₂-, -O-CH₂-, -SCH₂-, -SOCH₂-,

15 -SO₂CH₂-, -O-CX₂-, -O-CZ-, -NH-CZ-, -N=N-, -NH-SO₂-, -SO₂-NH-,

-CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH- or -NH-CO-NH-; and

Z is oxygen or sulfur; and

X is halo;

or an N-oxide thereof or a pharmaceutically acceptable salt thereof.

20 Compounds within the scope of the present invention possess useful properties, more particularly pharmaceutical properties. They are especially useful for inhibiting the production or physiological effects of TNF in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF).

25 Compounds within the scope of the present invention also inhibit cyclic AMP phosphodiesterase, and are useful in treating a disease state associated with pathological conditions that are modulated by inhibiting cyclic AMP phosphodiesterase, such disease states including inflammatory and autoimmune diseases, in particular type IV cyclic AMP phosphodiesterase.

30 The present invention is therefore also directed to their pharmaceutical use, pharmaceutical compositions containing the compounds, and methods for their preparation.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

5 Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means
10 that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more halo, cycloalkyl or cycloalkenyl. Exemplary alkyl groups include methyl, fluoromethyl, difluoromethyl, trifluoromethyl,
15 cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about
20 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more
25 halo. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about
30 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkynyl group may be substituted by one or more
35 halo. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.

"Oxaaliphatic" means a straight- or branched chain or non-aromatic monocyclic or multicyclic ring compound of about 2 to about 30 atoms wherein at least one of the atoms is oxygen and the others are carbon. The chain or the ring of the oxaaliphatic group may be saturated or unsaturated. The

- 5 oxaaliphatic group may be optionally substituted by one or more halo. Exemplary oxaaliphatic groups include alkoxyalkyl, alkenyloxyalkyl, alkynyloxyalkyl, oxacycloalkyl or oxacycloalkenyl groups as described herein.

- "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. Preferred monocyclic cycloalkyl rings
10 include cyclopentyl, fluorocyclopentyl, cyclohexyl and cycloheptyl; more preferred is cyclopentyl. The cycloalkyl group may be substituted by one or more halo, methylene ($H_2C=$) or alkyl. Exemplary multicyclic cycloalkyl rings include 1-decalin, adamant-(1- or 2-)yl and norbornyl.

- "Oxacycloalkyl" means a non-aromatic mono- or multicyclic ring system
15 of about 3 to about 10 ring atoms wherein at least one of the ring atoms is oxygen and the other ring atoms are carbon. Preferred rings include about 5 to about 8 ring atoms. Preferred rings have one ring atom which is oxygen. The oxacycloalkyl group may be substituted by one or more halo, methylene ($H_2C=$) or alkyl; more preferred is halo. Exemplary monocyclic rings include
20 tetrahydrofuryl, fluorotetrahydrofuryl and tetrahydropyranyl. Preferred is tetrahydrofuryl. Exemplary multicyclic cycloalkyl rings include 7-oxabicyclo[2.2.1]heptanyl and oxatricyclane. The oxacycloalkyl is attached to a oxy group by a direct bond or lower alkyl.

- "Oxacycloalkenyl" means a non-aromatic monocyclic or multicyclic ring
25 system of about 3 to about 10 ring atoms wherein at least one of the ring atoms is oxygen and the other ring atoms are carbon and the ring system contains a carbon-carbon double bond. Preferred rings include about 5 to about 8 ring atoms. Preferred rings have one ring atom which is oxygen. The oxacycloalkenyl group may be substituted by one or more halo, methylene
30 ($H_2C=$) or alkyl; more preferred is halo. Exemplary monocyclic rings include dihydrofuryl, fluorodihydrofuryl and dihydropyranyl. Preferred is dihydrofuryl. An exemplary multicyclic cycloalkyl ring is 7-oxabicyclo[2.2.1]-heptenyl. The oxacycloalkenyl is attached to a oxy group by a direct bond or lower alkyl.

- "Cyclothioalkyl" means a non-aromatic monocyclic or multicyclic ring
35 system of about 3 to about 10 ring atoms wherein at least one of the ring atoms is sulfur and the other ring atoms are carbon. Preferred rings include about 5

to about 6 ring atoms. Preferred rings have one ring atom which is sulfur. The cyclothioalkyl may be optionally substituted by one or more halo. Preferred monocyclic cyclothioalkyl rings include tetrahydrothiophenyl and tetrahydrothiopyranyl; more preferred is tetrahydrothiophenyl. The thio moiety of the cyclothioalkyl ring may also be optionally oxidized to the corresponding S-oxide or S,S-dioxide.

"Cyclothioalkenyl" means a non-aromatic monocyclic or multicyclic ring system having about 3 to about 10 ring atoms wherein at least one of the ring atoms is sulfur and the other ring atoms are carbon and the ring system contains a carbon-carbon double bond. Preferred rings include about 5 to about 6 ring atoms and wherein one of the ring atoms is sulfur. The cyclothioalkenyl may be optionally substituted by one or more halo. Preferred monocyclic cyclothioalkyl rings include dihydrothiophenyl and dihydrothiopyranyl; more preferred is dihydrothiophenyl. The thio moiety of the cyclothioalkyl may also be optionally oxidized to the corresponding S-oxide or S,S-dioxide

"Aromatic" means aryl or heteroaryl as defined below. Preferred aromatic groups include phenyl, halo substituted phenyl and azaheteroaryl.

"Aryl" means aromatic carbocyclic radical containing about 6 to about 10 carbon atoms. Exemplary aryl include phenyl or naphthyl, or phenyl or naphthyl substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes hydrogen, alkyl, aryl, aralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, carboxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, aralkylthio, Y¹Y²N-, Y¹Y²NCO- or Y¹Y²NSO₂-, where Y¹ and Y² are independently hydrogen, alkyl, aryl, and aralkyl. Preferred aryl group substituents include hydrogen, alkyl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, Y¹Y²N-, Y¹Y²NCO- and Y¹Y²NSO₂-, where Y¹ and Y² are independently hydrogen and alkyl.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. The heteroaryl may also be substituted by one or more aryl group substituents. "Azaheteroaryl" means a subclass of heteroaryl wherein one or more of the atoms in the ring system is/are replaced by nitrogen. Exemplary heteroaryl groups include pyrazinyl, furyl, thienyl,

pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, pyridazinyl, 1,2,4-triazinyl, quinolinyl, and isoquinolinyl. Preferred heteroaryl groups include pyrazinyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl and isothiazolyl. Preferred azaheteroaryl groups include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or
5 1,2,4-triazinyl.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously
10 defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and
15 palmitoyl.

"Aroyl" means an aryl-CO- group in which the alkyl group is as previously described. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as
20 previously described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Alkenyloxy" means an alkenyl-O- group in which the alkenyl group is as previously described. Exemplary alkenyloxy groups include allyloxy or
3-butenyloxy.

25 "Alkynyloxy" means an alkynyl-O- group in which the alkynyl group is as previously described. Exemplary alkynyloxy groups include propynyloxy or 3-butyloxy.

"Alkoxyalkyl" means alkyl-O-alkyl group wherein the alkyl groups are as described previously.

30 "Alkenyloxyalkyl" means alkenyl-O-alkyl group wherein the alkyl and alkenyl groups are as described previously.

"Alkynyloxyalkyl" means alkynyl-O-alkyl group wherein the alkyl and alkenyl groups are as described previously.

35 "Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl groups is as previously described. Exemplary aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

5 "Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

10 "Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. An exemplary aralkylthio group is benzylthio.

"Y¹Y²N-" means a substituted or unsubstituted amino group, wherein Y¹ and Y² are as previously described. Exemplary groups include amino (H₂N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

15 "Alkoxy carbonyl" means an alkyl-O-CO- group. Exemplary alkoxy carbonyl groups include methoxy- and ethoxy carbonyl.

"Aryloxy carbonyl" means an aryl-O-CO- group. Exemplary aryloxy carbonyl groups include phenoxy- and naphthoxy carbonyl.

20 "Aralkoxy carbonyl" means an aralkyl-O-CO- group. An exemplary aralkoxy carbonyl group is benzyloxy carbonyl.

"Y¹Y²NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y¹ and Y² are as previously described. Exemplary groups are carbamoyl (H₂NCO-) and dimethylcarbamoyl (Me₂NCO-).

25 "Y¹Y²NSO₂-" means a substituted or unsubstituted sulfamoyl group, wherein Y¹ and Y² are as previously described. Exemplary groups are sulfamoyl (H₂NSO₂-) and dimethylsulfamoyl (Me₂NSO₂-).

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

30 "Alkylsulfonyl" means an alkyl-SO₂- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an aryl-SO₂- group.

"Arylsulfinyl" means an aryl-SO- group.

35 "Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo; more preferred are fluoro or chloro, and further preferred is fluoro.

Preferred Embodiments

A compound of formula I is preferred for use in treating a disease state associated with a physiologically detrimental excess of tumor necrosis factor.

Disease states associated with pathological conditions that are modulated by inhibiting cyclic AMP phosphodiesterase are also preferably
5 treated with a compound of formula I.

According to the compound aspect of the invention, preferred compounds are described by formula I wherein R^2 is tetrahydrofuryl or tetrahydropyranyl; more preferably R^2 is tetrahydro-3-furyl.

According to a further aspect of the invention, preferred compounds of
10 formula I are described wherein Q^1 and Q^2 and Q^3 all represent CH, more preferred compounds of formula I are described wherein Q^1 and Q^2 are independently nitrogen or CX and Q^3 is CH. CX is preferably CF. Further preferred are compounds wherein Q^2 is CF, or nitrogen and N-oxides thereof.

According to a further aspect of the invention, more preferred
15 compounds of formula I are described wherein Z^1 is oxygen.

Compounds of the invention wherein R^1 is unsubstituted or substituted by halo, preferably fluoro, are also preferred. It is further preferred that the halo substitution is on a position of R^1 that is attached respectively to Z^1 .

Among the compounds of the invention wherein R^3 is substituted
20 phenyl, the phenyl group is preferably substituted on the 2-position or on both the 2- and 6-positions.

Similarly, among compounds of the invention where R^3 is substituted heteroaryl, the heteroaryl group is preferably substituted on one or both, more preferably on both, of the positions adjacent to a position of R^3 that is attached
25 to Z^2 . Further preferred are compounds wherein R^3 is a 3,5-dihalopyrid-4-yl moiety or an N-oxide thereof.

Special embodiments of the compounds of the invention include those of formula I wherein Z^2 is -CZNH- or -CZCH₂-, more preferably wherein Z is oxygen; and R^2 is oxacycloalkyl. More preferred are compounds wherein Z^2 is
30 -CONH-; and R^2 is tetrahydrofuryl.

Another special embodiment of the compounds of the invention include those of formula I wherein R^1 is lower alkyl optionally substituted by halo; and R^2 is oxacycloalkyl, more preferably tetrahydrofuryl.

Another special embodiment of the compounds of the present invention
35 include those wherein R^2 is oxacycloalkyl, more preferably tetrahydrofuryl; and R^3 is aryl or heteroaryl, more preferably phenyl or pyridyl, each of which is substituted on one or both, more preferably on both, of the positions adjacent to

the position of R^3 that is attached to Z^2 , and preferably the substituents are halo.

Another special embodiment of the compounds of the present invention include those wherein R^2 is oxacycloalkyl, more preferably tetrahydrofuryl; and
 5 Z^1 is oxygen.

Another special embodiment of the compounds of the present invention include those wherein R^2 is oxacycloalkyl, more preferably tetrahydrofuryl; and Z^1 is oxygen.

A compound of formula I wherein R^2 is oxacycloalkyl, more preferably
 10 tetrahydrofuryl; and Z^2 is $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{-CZ}-$, $-\text{CZ-CZ}-$, $-\text{CH}_2\text{-NH}-$, $-\text{CH}_2\text{-O}-$, $-\text{CH}_2\text{-S}-$, $-\text{CX}_2\text{-O}-$, $-\text{NH-CH}_2-$, $-\text{O-CH}_2-$, $-\text{SCH}_2-$, $-\text{SOCH}_2-$, $-\text{SO}_2\text{CH}_2-$, $-\text{O-CX}_2-$, $-\text{O-CZ}-$, $-\text{NH-CZ}-$, $-\text{N=N-}$, $-\text{NH-SO}_2-$, $-\text{SO}_2\text{-NH-}$, $-\text{CZ-CZ-NH-}$, $-\text{NH-CO-O-}$, $-\text{O-CO-NH-}$ or $-\text{NH-CO-NH-}$, more preferably $-\text{O-CH}_2-$, $-\text{O-CZ}-$, $-\text{NH-CZ}-$, $-\text{NH-CO-NH-}$, $-\text{CH}_2\text{-NH-}$, $-\text{CH}=\text{CH}-$, $-\text{SO}_2\text{-NH-}$,
 15 $-\text{N=N-}$ or $-\text{CZ-CZ-}$, is another special embodiment of the compounds of the present invention.

Preferred compounds for use according to the invention are selected from the following:

- (A) (\pm) -N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 (B) (\pm) -N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)benzamide;
- (C) (\pm) -N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 (D) (\pm) -N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (E) (\pm) -N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AF) N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 (AG) N-(2-chloro-6-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AH) N-(2-trifluoromethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AI) N-(2,4,6-trichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 (AJ) N-(2,6-dibromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- (AK) N-(2-chloro-6-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AL) N-(2,6-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AM) N-(2-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 (AN) N-phenyl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AO) N-(2-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AP) N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AQ) N-(3-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AR) N-(4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 (AS) N-(2,6-dimethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AT) N-(2-methylthiophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AU) N-(2-bromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AV) N-(2-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 (AW) N-(2-aminosulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AX) N-(2-benzoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AY) N-(2-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (AZ) N-(2,5-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 (BA) N-(3-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BB) N-(2-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BC) N-(2-dimethylaminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BD) N-(2-acetylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 (BE) N-(2-hydroxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BG) N-(2-methylsulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BK) N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)benzamide;
- 30 (BL) N-(2,6-difluorophenyl)-3-(2-ethoxyethoxy)-4-methoxybenzamide; and
- (BM) N-(2,6-difluorophenyl)-4-methoxy-3-(2-methoxyethoxy)benzamide;
- (BO) N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- (BY) N-(4-chloropyrid-3-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (BZ) N-pyrid-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 (CA) N-pyrazin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (CB) N-pyrimidin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (CC) N-(3-methylpyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- (CD) N-pyrid-3-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(CE) N-(3-chloropyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(CF) N-(3-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(CG) N-pyrid-4-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
5 (CJ) N-(3,5-dimethylisoxazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(DF) 3-[2-(2-butoxyethoxy)ethoxy]-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide;
(DG) N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
10 (DH) N-(3,5-dichloropyrid-4-yl)-3-(2-ethoxyethoxy)-4-methoxybenzamide;
(DI) N-(3,5-dimethylpyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(DJ) N-(2,6-dichloro-4-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
15 (DK) N-(2,6-dichloro-4-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(DL) N-(2,3,5-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
20 (DM) N-(2,6-dichloro-4-ethoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(DN) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
(DO) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
25 (DP) N-(2,6-dichloro-4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(DQ) N-(3,5-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
30 (DR) N-(2,6-dichlorophenyl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
(DS) N-(2,6-dichlorophenyl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
(DT) N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-methoxybenzamide;
35 (DU) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-2H-pyran-2-methyloxy)benzamide;

- (DV) N-(3-bromo-5-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (DW) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxyprop-2-oxy)benzamide;
- 5 (DX) N-(3,5-dichloropyrid-4-yl)-3-(2-isopropoxyethoxy)-4-methoxybenzamide;
- (DY) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(3-methoxy-1-butoxy)benzamide;
- (EB) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- 10 (ED) N-(2,6-dichloro-4-aminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (EF) N-(2,6-dichloro-4-acetylaminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (EJ) N-(2,6-dichloro-4-formylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 (EL) N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide;
- (EN) sodium salt of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 (EQ) N-(2,4,6-trifluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (ER) N-(2,6-dichloro-4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (ET) N-(2,6-dichlorophenyl)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;
- 25 (FA) N-(4,6-dichloropyrimid-5-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (FB) N-(2,3,5,6-tetrafluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (FC) N-(3,5-dichloro-2,6-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 (FD) N-(5-cyano-3-methylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (FE) N-(2,6-dichloro-4-carbamoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 35 (FF) N-(3-chloro-2,5,6-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (FH) N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(2-ethoxyethoxy)benzamide;

- (FL) N-(4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(FM) N-(3-methyl-5-bromoisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
(FN) N-(3,5-dimethylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
5 (FP) N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;
(FR) N-(3,5-difluoropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;
10 (FV) N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;
(FW) N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzamide;
(FX) N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]-
15 heptan-6-oxy]benzamide;
(FZ) N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzamide;
(GB) N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzamide;
20 (GD) N-(3,5-dichloropyrid-4-yl)-4-(fluoromethylthio)-3-(tetrahydro-3-furyloxy)benzamide;
(GF) 2',6'-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;
(GH) 3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;
25 (GJ) 3,5-dichloro-4-(2-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-oxoethyl)pyridine-N-oxide;
(GL) 2-(3-chloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;
(GN) 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(4-pyridyl)ethanone;
30 (GP) 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-phenylethanone;
(GR) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzamide;
(GT) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)benzamide;
35 (GV) N-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2,6-dichlorobenzamide;
(GX) N-[4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2,6-difluorobenzamide;

- (GZ) N-(2,6-dichlorophenyl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-urea;
- (HB) N-(3,5-dichloropyrid-4-yl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)urea;
- 5 (HD) 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl 2,6-dichlorobenzoate;
- (HF) 2,6-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ether;
- (HH) N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzylamine;
- (HJ) trans-2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- 10 (HL) trans-2-(2,6-difluorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- (HN) 1-[(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2-(pyrid-4-yl)ethane-1,2-dione;
- (HP) trans-2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)diazene;
- 15 (HS) 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-c-1-oxo-r-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- (HT) trans-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- 20 (HV) N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzene-sulfonamide;
- (HX) N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzamide;
- (HZ) N-(3,5-dichloropyrid-4-yl)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-
- 25 [5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide;
- (IB) N-(3,5-difluoropyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- (ID) N-(3,5-difluoro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- 30 (IF) N-(3,5-dichloro-pyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- (IH) N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- (IJ) N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(7-oxa-
- 35 bicyclo[2.2.1]heptan-2-oxy)benzamide;
- (IL) N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide;

- (IN) N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[2-(prop-2-yn-1-oxy)ethoxy]-benzamide;
- (IP) N-(3,5-dichloro-1-oxido-4-pyridinio)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]-decan-8-oxy)-4-methoxybenzamide;
- 5 (IR) N-(3,5-dichloropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;
- (IT) N-(3,5-difluoropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;
- (IV) N-(3,5-dichloropyrid-4-yl)-3-(3-methoxybutoxy)-4-
- 10 (methylthio)benzamide;
- (IX) 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone;
- (IZ) 2-(3,5-dichloropyrid-4-yl)-1-[4-(methylthio)-3-(tetrahydro-3-furyloxy)phenyl]ethanone;
- 15 (JB) 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)-phenyl)ethanone;
- (JD) 2-(3,5-dichloropyrid-4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)-phenyl)ethanone;
- (JF) 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone;
- 20 (JH) 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)-ethanone;
- (JJ) 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;
- 25 (JL) 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanone;
- (JN) 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]-heptan-2-oxy)phenyl)ethanone;
- (JP) 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-[4-difluoromethoxy-3-(7-
- 30 oxabicyclo-[2.2.1]heptan-2-oxy)phenyl]ethanone;
- (JR) 2-(3,5-dichloro-4-pyridyl)-1-[3-(2-isopropoxyethoxy)-4-methoxyphenyl]-ethanone;
- (JT) 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone.
- 35 (JV) 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone;

- (JX) 3,5-dichloro-4-(4-methoxy-3-(tetrahydro-3-furyloxy)phenoxy-methyl)pyridine;
- (JZ) N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(7-oxabicyclo[2.2.1]-heptan-2-oxy)benzamide;
- 5 (KB) N-(3,5-dichloropyrid-4-yl)-6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (KD) N-(3,5-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- (KF) N-(2,6-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- 10 (KH) N-(3,5-difluoropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- (KJ) N-(3,5-dichloropyrid-4-yl)-5-methoxy-6-(tetrahydro-3-furyloxy)pyridine-2-carboxamide;
- 15 (KL) N-(3,5-dimethylisoxazol-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)-nicotinamide;
- (KN) 2-(3,5-dichloropyrid-4-yl)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- (KT) N-(3,5-dichloropyrid-4-yl)-6-(methylthio)-5-(tetrahydro-3-furyloxy)-nicotinamide;
- 20 (KU) 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- (KV) N-(3,5-dichloropyrid-4-yl)-5-(1-methoxyprop-2-oxy)-6-(methylthio)-nicotinamide;
- 25 (KW) 2-(3,5-dichloropyrid-4-yl)-1-[5-(1-methoxyprop-2-oxy)-6-(methylthio)pyrid-3-yl]-ethanone;
- (ZA) (S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (ZB) (R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 30 (ZC) (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide;
- (ZD) (±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 35 (ZE) (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

- (ZF) (\pm)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (ZG) (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 5 (ZH) (\pm)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (ZI) (\pm)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone; and
- (ZJ) (\pm)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone.
- 10

A group of preferred compounds includes A, B, C, D, E, DN, DO, DW, DQ, FP, GH, GJ, GT, IL, IX, JH, JJ, JL, JN, JP, JZ, KB, KD, KH, ZA, ZB, ZC, ZD, ZE, ZF, ZG, ZH, ZI and ZJ.

- A group of especially preferred compounds includes A, C, D, E, DW, JH, JJ, ZA, ZB, ZC, ZD, ZE, ZF, ZG, ZH, ZI and ZJ.
- 15

Another group of preferred compounds includes A, C, D, E, DN, DO, DQ, FP, GH, GJ, GT, IL, IX, JL, JN, JP, JZ, KB, KD and KH.

Another group of especially preferred compounds includes A, C, D and E.

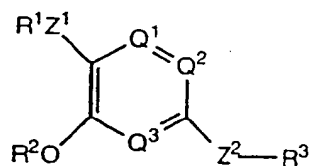
- 20 A particularly preferred compound is ZG.

The letters A to ZJ are allocated to compounds for easy reference in this specification.

Compounds of formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

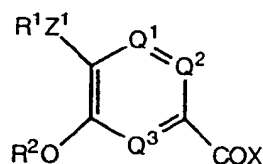
Thus, according to a feature of the invention, compounds of formula I

5



wherein R¹, R², R³, Q¹, Q², Q³ and Z¹ are as hereinbefore defined, Z² represents a -CZNH- linkage, and Z represents oxygen, are prepared by the reaction of compounds of formula II

10



II

hereinafter depicted, wherein R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined and X represents halo, e.g. bromo or, preferably, chloro, with compounds of the formula III

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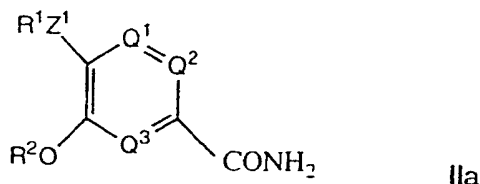
III

wherein R³ is as hereinbefore defined, preferably in the presence of a base such as an alkali metal hydride, e.g. sodium hydride, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature or at the melting point of the reaction mixture.

20

As a further feature of the invention, compounds of formula I, wherein R¹, R², R³, Q¹, Q² and Q³ are as hereinbefore defined, Z and Z¹ are oxygen, and Z² represents a -CZNH- linkage, are prepared by the reaction of compounds of formula IIa:-

25



wherein R^1 , R^2 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z and Z^1 are oxygen, with compounds of the formula Va:-



wherein R^3 and X are as hereinbefore defined, preferably X is chloro, and preferably the preparation takes place in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal alkoxide, e.g. potassium t-butoxide, an alkali metal hydroxide, e.g. sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from $0^\circ C$ to the reflux temperature.

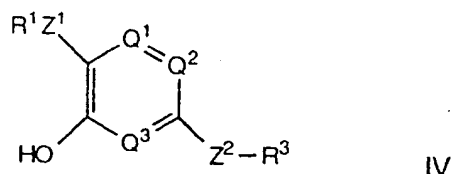
1 5 As a further feature of the invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z and Z^1 are oxygen, and Z^2 represents a -CZNH- linkage, are prepared by the reaction of compounds of formula II as hereinbefore described, with a compound of the formula IIIa:-



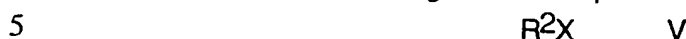
wherein R^3 is as hereinbefore defined, and R^4 represents an alkyl or cycloalkyl group containing up to 5 carbon atoms, preferably a methyl group, preferably in the presence of a base, for example an alkali metal hydride, such as sodium hydride, or an amine, preferably a tertiary amine, such as triethylamine, in an inert solvent, for example toluene, dimethylformamide, or an ether, such as tetrahydrofuran or diethyl ether, at a temperature from about $0^\circ C$ to reflux, then with a second base, for example an amine, such as piperidine.

3 0 As a further feature of the invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a -CZNH- linkage, are prepared by the reaction of compounds of formula IV hereinafter depicted,

- 25 -

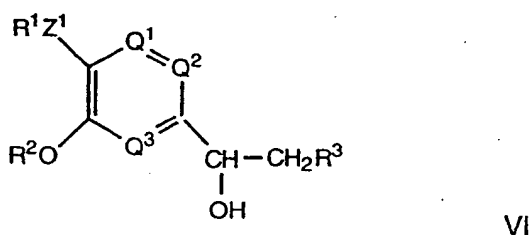


wherein R^1 , R^3 , Z , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a -CZNH- linkage, with compounds of the formula V



wherein R^2 is as hereinbefore defined, preferably, X is as hereinbefore defined or p-toluenesulfonate, preferably X is bromo, and preferably the preparation takes place in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or carbonate, e.g. sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

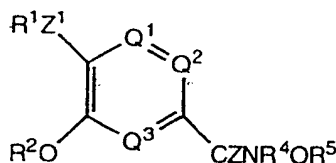
As a further feature of the invention, compounds of formula I, wherein
15 R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a -CZCH₂- linkage, and Z represents oxygen, are prepared from compounds of formula VI



20 wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, by oxidation by the application or adaptation of known methods. The oxidation is carried out, for example, by reaction with oxalyl chloride and dimethyl sulfoxide, in a solvent such as dichloromethane, and preferably at a
25 temperature lower than -65°C . Alternatively, the oxidation is carried out by reaction with chromium trioxide in the presence of 3,5-dimethylpyrazole.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore

defined, Z^2 represents a $-CZCH_2-$ linkage, and preferably those wherein Z represents oxygen, are prepared from compounds of formula VII



VII

5

wherein R^1 , R^2 , Z, Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and R^4 and R^5 represent lower alkyl, e.g. methyl, groups, by coupling with compounds of the formula VIII wherein R^3 is as hereinbefore defined, in the presence of a

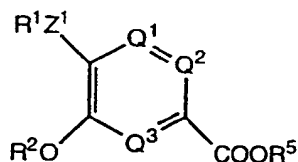


VIII

- 1 0 strong base such as lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), preferably at a low temperature.

As a further feature of the invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a $-CZCH_2-$ linkage, and Z represents oxygen, are prepared from compounds of

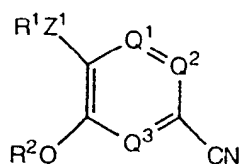
- 1 5 formula VIIa:-



VIIa

- 2 0 wherein R^1 , R^2 , R^5 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, by coupling with compounds of the formula VIII as hereinbefore defined, in the presence of a strong base such as lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), preferably at a low temperature.

- 2 5 According to a feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a $-CZCH_2-$ linkage, and Z represents oxygen, are prepared by the reaction of compounds of formula IX wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3



IX

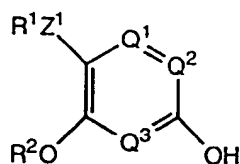
are as hereinbefore defined, with compounds of the formula X



5 wherein R³ and X are as hereinbefore defined.

As a further feature of the invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -O-CH₂- linkage, are prepared by the reaction of compounds of the formula XI

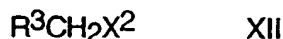
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XI

wherein R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined, with compounds of the formula XII wherein R³ and X are as hereinbefore defined,

15



and X is preferably chloro, preferably takes place in the presence of a base such as an alkali metal carbonate, e.g. potassium carbonate, preferably in a solvent such as dimethylformamide:

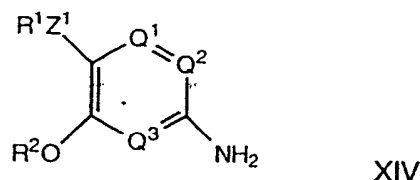
According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -O-CO- linkage are prepared by the reaction of compounds of formula XI above, wherein R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined, with compounds of the formula XIII wherein R³



25 and X are as hereinbefore defined, and X is preferably chloro, preferably in the presence of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined

and Z^2 represents an -NH-CO- linkage are prepared by the reaction of compounds of formula XIV wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as



5

hereinbefore defined, with compounds of formula XIII above, wherein R^3 and X^2 are as hereinbefore defined, preferably in the presence of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

10

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents an -NH-CO-NH- linkage, are prepared by the reaction of compounds of formula XIV above, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of the formula XV wherein R^3 is as

15



hereinbefore defined, preferably in the presence of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

20

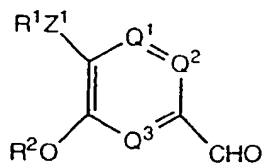
According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents an -NH-CO-NH- linkage are prepared by the reaction of compounds of formula XIV, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of the formula III above, wherein R^3 is as hereinbefore defined, and phosgene or a source thereof, preferably by reacting the compound of formula XIV with phosgene or, preferably, bis(trichloromethyl) carbonate, and by then reacting the product of that reaction with the cation derived from the compound of formula III (for example by reaction with a base such as sodium hydride). The reactions are preferably carried out in suitable solvents such as dichloromethane and tetrahydrofuran.

25

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a -CH₂-NH- linkage, are prepared by the reaction of compounds of formula XVI wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as

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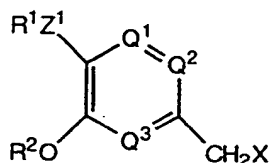
- 29 -



XVI

hereinbefore defined, with compounds of formula III above, wherein R^3 is as hereinbefore defined, followed by reduction with a compound such as sodium cyanoborohydride. This process is especially suitable for compounds wherein R^3 represents an optionally substituted phenyl or naphthyl group.

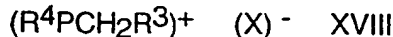
According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-CH_2-NH-$ linkage, are prepared by the reaction of compounds of formula XVII wherein X , R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as



XVII

hereinbefore defined, and X is preferably bromo, with compounds of formula above, wherein R^3 is as hereinbefore defined, preferably in the presence of a base such as sodium hydride. This process is especially suitable for compounds wherein R^3 represents an optionally substituted heteroaryl group.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $trans-CH=CH-$ linkage are prepared by the reaction of compounds of formula XVI above, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with the reaction product of a compound of the formula XVIII wherein R^3 is as hereinbefore defined, R^4 represents an aryl, such as

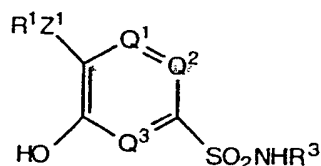


phenyl group, and X represents halo, preferably bromo, with a base such as an alkali metal alkoxide, e.g. potassium *t*-butoxide. The reaction is preferably carried out in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined

- 30 -

and Z^2 represents an $-SO_2-NH-$ linkage are prepared by the reaction of compounds of formula XIX wherein R^1 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as



XIX

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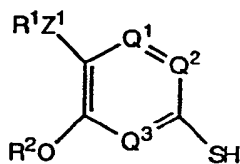
hereinbefore defined, with compounds of the formula V wherein R^2 and X are



as hereinbefore defined, preferably after treatment with a base such as sodium hydride, preferably in a solvent such as dimethylformamide.

10

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents an $-S-CH_2-$ linkage are prepared by the reaction of compounds of formula XX wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as



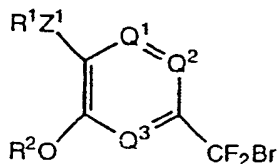
XX

15

hereinbefore defined, with compounds of formula XII above, wherein R^2 and X are as hereinbefore defined, and preferably X is bromo, preferably after reaction with a base such as an alkali metal alkoxide, e.g. sodium methoxide.

20

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-CF_2-O-$ linkage, are prepared by the reaction of compounds of formula XXI wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are wherein



XXI

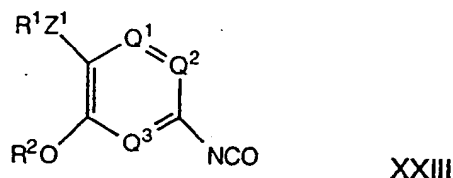
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R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined, with compounds of the formula XXII



wherein R³ is as hereinbefore defined, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -NH-CO-O- linkage, are prepared by the reaction of compounds of formula XXIII wherein R¹, R², Z¹, Q¹, Q² and Q³ are as



hereinbefore defined, with compounds of formula XXII above, wherein R³ is as hereinbefore defined, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -NH-CH₂- linkage, are prepared by the reaction of compounds of formula XIV above, wherein R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined, with compounds of the formula XXIV wherein R³ is



as hereinbefore defined, preferably with the aid of a reducing agent such as sodium cyanoborohydride.

According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -NH-SO₂- linkage, are prepared by the reaction of compounds of formula XIV above, wherein R¹, R², Z¹, Q¹, Q² and Q³ are as hereinbefore defined, with compounds of the formula XXV wherein R³ and X



are as hereinbefore defined, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R¹, R², R³, Z¹, Q¹, Q² and Q³ are as hereinbefore defined and Z² represents an -O-CO-NH- linkage, are prepared by the reaction of

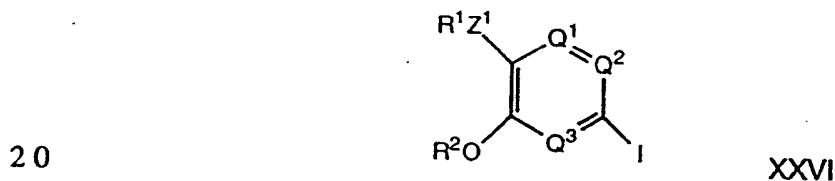
compounds of formula XI above, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of formula XV above, wherein R^3 is as hereinbefore defined, or with a compound of formula III above, wherein R^3 is as hereinbefore defined, and phosgene or, preferably, bis(trichloromethyl) carbonate, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents an $-O-CF_2-$ linkage, are prepared by the reaction of compounds of formula XI above, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of the formula XXVa wherein R^3 is

$$R^3CF_2Br \quad \text{XXVa}$$

as hereinbefore defined, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents an ethynyl linkage, are prepared by the reaction of compounds of formula XXVI hereinafter depicted, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2



and Q^3 are as hereinbefore defined, with compounds of the formula XXVII

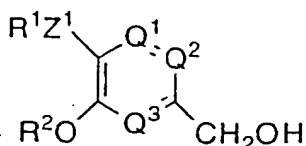


wherein R^3 is as hereinbefore defined and X^1 represents an ethynyl group.

25 Preferably the reaction is carried out with the aid of a catalyst, e.g. palladium on carbon, and cuprous iodide, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-CH_2-O-$ linkage, are prepared by the reaction of compounds of formula XXVIII:-

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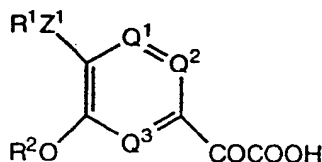


XXVIII

wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of the formula V above, wherein R^3 and X are as hereinbefore defined, preferably with the aid of a base such as an alkali metal alkoxide, e.g. potassium t-butoxide. The reaction is preferably carried out in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-\text{CH}_2\text{O}-$ linkage, are prepared by the reaction of compounds of formula XVII above, wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 , Q^3 and X are as hereinbefore defined, with compounds of formula XXII above, wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as an alkali metal alkoxide, e.g. potassium t-butoxide.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-\text{CO}-\text{CO}-\text{NH}-$ linkage, are prepared by the reaction of compounds of formula XXIX wherein R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as



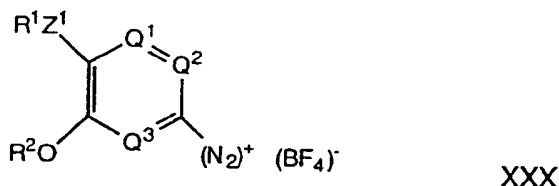
XXIX

hereinbefore defined, with dichloromethyl methyl ether in dichloromethane, followed by reaction with compounds of formula III above, wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-\text{CO}-\text{CO}-$ linkage, are prepared by the oxidation of compounds of formula VI above, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, for example by reaction with pyridinium dichromate, preferably in a solvent such as dichloromethane. This reaction is particularly

suitable for compounds wherein R^3 represents a heteroaryl, preferably an optionally substituted pyridyl, group.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a trans $-N=N-$ linkage, are prepared by the reaction of compounds of formula XXX wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as

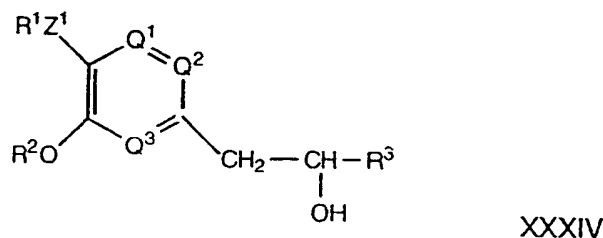


hereinbefore defined, with compounds of the formula XXXI wherein R^3 is as
 R^3H XXXI
 hereinbefore defined, preferably with the aid of a base such as lithium diisopropylamide.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z represents a $-CH_2-S-$ linkage, are prepared by the reaction of compounds of formula XVII, wherein X , R^1 , R^2 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, with compounds of the formula XXXIII wherein R^3
 R^3-SH XXXIII

is as hereinbefore defined, preferably with the aid of a base such as an alkali metal carbonate, e.g. potassium carbonate.

According to a further feature of the present invention, compounds of formula I, wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined and Z^2 represents a $-CH_2-CO-$ linkage, are prepared by the oxidation of compounds of formula XXXIV



wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined. The oxidation is carried out, for example, by reaction with oxalyl chloride and dimethyl sulfoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than -65°C . Alternatively, the oxidation is carried out by reaction with chromium trioxide in the presence of 3,5-dimethylpyrazole.

According to a further feature of the present invention, compounds of general formula I are prepared by interconversion of other compounds of general formula I.

For example, compounds of formula I wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, and Z^2 represents a cis $-\text{C}=\text{C}-$ or cis $-\text{N}=\text{N}-$ linkage are prepared by the action of ultraviolet radiation upon their trans-isomers.

As another example, compounds of formula I wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^1 preferably represents oxygen, and Z^2 represents an $-\text{SO}-\text{CH}_2-$ linkage are prepared by the oxidation of corresponding compounds wherein Z^2 represents an $-\text{S}-\text{CH}_2-$ linkage. For example, the oxidation can be carried out by means of potassium hydrogen peroxomonosulfate in a medium such as aqueous methanol.

As another example, compounds of formula I wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^1 preferably represents oxygen, and Z^2 represents an $-\text{SO}_2-\text{CH}_2-$ linkage are prepared by the oxidation of corresponding compounds wherein Z^2 represents an $-\text{S}-\text{CH}_2-$ linkage. For example, the oxidation can be carried out by means of sodium iodate in a medium such as aqueous methanol.

As another example, compounds of formula I wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a $-\text{CZCH}_2-$ linkage, and Z represents sulfur are prepared from compounds of formula I wherein R^1 , R^2 , R^3 , Z^1 , Q^1 , Q^2 and Q^3 are as hereinbefore defined, Z^2 represents a $-\text{CZCH}_2-$ linkage, and Z represents oxygen, by reaction with phosphorus pentasulfide or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, preferably in a solvent such as pyridine or toluene, and preferably at a temperature from 0°C to the reflux temperature.

As another example, compounds of formula I wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 , Z, Z^1 and Z^2 are as hereinbefore defined, Z and Z^1 preferably each represent oxygen, and R^3 is as hereinbefore defined and contains an alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl group, are prepared by the oxidation of the corresponding compounds of formula I wherein R^1 , R^2 , Q^1 , Q^2 ,

Q³, Z, Z¹ and Z² are as hereinbefore defined and R³ is as hereinbefore defined and contains an alkylthio or arylthio group, preferably by means of reaction with a peroxyacid, e.g., 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature. Alternatively, the oxidation is carried out by reaction with a peroxomonosulfate, e.g. potassium peroxomonosulfate, conveniently in a solvent such as methanol, buffered to about pH 5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R²O- contains a carbon-carbon double bond between its beta- and gamma-carbon atoms, e.g. a cyclopent-2-enyloxy group.

As another example, compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined, and Z is preferably oxygen, and R³ is as hereinbefore defined and contains a hydroxymethyl group are prepared by the reduction of the corresponding compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z¹ and Z² are as hereinbefore defined and R³ is as hereinbefore defined and contains an aryloxycarbonyl or, preferably, alkoxycarbonyl group, preferably by means of reaction with an alkali metal borohydride, preferably in an inert solvent, e.g. tetrahydrofuran, preferably at or near room temperature.

As another example, compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined, Z preferably being an oxygen atom, and R³ is as hereinbefore defined and contains a formyl group are prepared by the oxidation of the corresponding compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined and R³ is as hereinbefore defined and contains a hydroxymethyl group, for example by reaction with oxalyl chloride and dimethyl sulfoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than -65°C, or, preferably, by reaction with a complex of sulfur trioxide with an amine such as pyridine, preferably in the presence of an amine such as triethylamine, preferably at or near room temperature.

As another example, compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined, and Z is preferably oxygen, and R³ is as hereinbefore defined and contains an amino group are prepared by the reduction of the corresponding compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined and R³ is as hereinbefore defined and contains a nitro group, preferably by means of reaction with iron in acidic conditions, e.g. in acetic acid, preferably at or above room temperature,

more especially at the reflux temperature. Alternatively the reduction are carried out by reaction with hydrazine hydrate in the presence of ferric chloride and activated carbon, conveniently in a solvent such as methanol, at temperatures between about 25°C and 80°C. This latter method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R²O- contains a carbon-carbon double bond between its beta and gamma-carbon atoms, e.g. a cyclopent-2-enyloxy group.

As another example, compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined, and Z is preferably oxygen, and R³ is as hereinbefore defined and contains an alkanoylamino or aroylamino group are prepared from compounds of formula I wherein R¹, R², Q¹, Q², Q³, Z, Z¹ and Z² are as hereinbefore defined and R³ is as hereinbefore defined and contains an amino group, preferably by means of reaction with the appropriate acid halide or acid anhydride in the presence of a tertiary base such as triethylamine, optionally in an inert solvent, and preferably at a temperature from 0°C to the reflux temperature.

As another example, the compounds of formula I wherein Q¹, Q² or Q³ represents a nitrogen atom and/or R³ represents a heteroaryl group containing one or more nitrogen ring atoms, Z and Z¹ each preferably representing oxygen atoms, can be oxidised to the corresponding N-oxides. The oxidation may be carried out by means of reaction with a mixture of hydrogen peroxide and an organic acid, e.g. acetic acid, preferably at or above room temperature at 60-90°C. Alternatively, the oxidation is carried out by reacting a peracid, for example *m*-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature. Alternatively, the oxidation is carried out by reaction with hydrogen peroxide in the presence of sodium tungstate at temperatures between room temperature and about 60°C. This last method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R²O- contains a carbon-carbon double bond between its beta- and gamma-carbon atoms, e.g. a cyclopent-2-enyloxy group.

As another example, an N-oxide group, in an N-oxide of a compound of formula I wherein Q¹, Q² or Q³ represents a nitrogen atom and/or R³ represents a heteroaryl group containing one or more nitrogen ring atoms, Z and Z¹ each preferably representing oxygen, can be reduced to a nitrogen atom. More particularly, one of the N-oxide groups in an N-oxide of a compound of formula I wherein Q¹, Q² or Q³ represents a nitrogen atom in its

oxidised form and R^3 represents a heteroaryl group containing one or more nitrogen ring atoms in its oxidised form, can be reduced to a nitrogen atom. For example, the N-oxide group in the group R^3 in such a compound can be reduced to a nitrogen leaving the other N-oxide group unchanged. The
5 ~~reduction of an N-oxide group may be carried out by reaction with~~
diphosphorus tetraiodide in an inert solvent, such as dichloromethane, preferably at or near room temperature, or by reaction with a chlorotrialkylsilane, preferably chlorotrimethylsilane, in the presence of zinc and an alkali metal iodide, e.g. potassium iodide, in an inert solvent, e.g.
10 acetonitrile, at a temperature between about 0°C and about room temperature, preferably below room temperature.

As another example, compounds of formula I wherein R^1 is as hereinbefore defined and is substituted on its alpha-carbon atom by fluorine and Z^1 is sulfur, and Q^1 , Q^2 , Q^3 , R^3 and Z^2 as hereinbefore defined, are
15 prepared by the reaction of xenon difluoride with corresponding compounds of formula I wherein said alpha-carbon atoms carry hydrogen atoms instead of said fluorine atoms. The reaction is conveniently carried out in a solvent, such as dichloromethane, in the presence of a molecular sieve, and in an inert atmosphere, at a low temperature, e.g. at or near 0°C.

20 As another example, compounds of formula I wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 , Z , Z^1 and Z^2 are as hereinbefore defined, and R^3 represents a heteroaryl group containing one or more nitrogen ring atoms but carrying no halogen substituents, are prepared by the reduction of the corresponding compounds of formula I wherein R^3 does carry one or more halogen, e.g. chlorine,
25 substituents, for example by means of ammonium formate in the presence of a palladium catalyst.

It will be apparent to those skilled in the art that compounds of the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will also be
30 apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. The present invention comprises the individual geometrical isomers and stereoisomers and mixtures thereof.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and
35 recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on TNF and PDE inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis- β -hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an

organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods.

5 For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient
10 form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the
15 beneficial inhibitory effects on TNF and PDE inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum
20 hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

25 Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as
30 methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

35 Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran,

nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods.

- 5 For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

- 10 As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention wherein R^3 represents a nitrogen-containing heteroaryl group and/or wherein R^3 contains an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein R^2 is other than an acid labile group.

- 15 As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

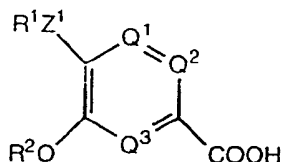
- 20 It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism and optical isomerism. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl or diazenyl moieties. All isomers within formula I, and their mixtures, are within the scope of the invention.

- 25 Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

- 30 The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

For example, compounds of formula II, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, are prepared from compounds of formula XXXV wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, by the

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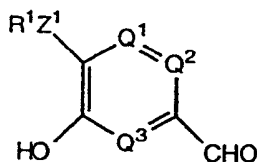


XXXV

application or adaptation of known methods for the preparation of acid halides from carboxylic acids. For example, when X in compound of formula II
 5 represents a chloro, the reaction can be carried out by means of thionyl chloride or, preferably, oxalyl chloride in the presence of triethylamine.

Compounds of formula XXXV, wherein R¹, R², Q¹, Q², Q³ and Z¹ are as hereinbefore defined, are prepared by the oxidation of compounds of formula XVI above, wherein R¹, R², Q¹, Q², Q³ and Z¹ are as hereinbefore defined,
 10 e.g. by means of reaction with potassium permanganate, or with a mixture of sulfamic acid and sodium chlorite in acetic acid, or with sodium chlorite in the presence of sodium dihydrogen phosphate.

Compounds of formula XVI, wherein R¹, R², Q¹, Q², Q³ and Z¹ are as hereinbefore defined, are prepared from compounds of formula XXXVI
 15



XXXVI

wherein R¹, Q¹, Q², Q³ and Z¹ are as hereinbefore defined, by reaction with compounds of the formula:

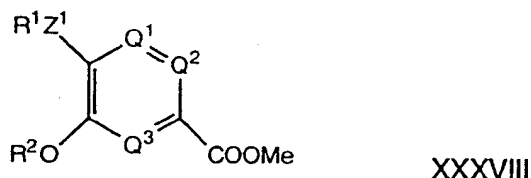


wherein R² and X are as hereinbefore defined, and X is preferably bromo, preferably in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or carbonate, e.g. sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or
 25 pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature, or alternatively by reaction with compounds of the formula XXXVII



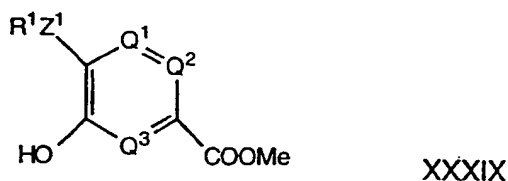
wherein R^2 is as hereinbefore defined, preferably in the presence of a compound such as diisopropyl azodicarboxylate.

Alternatively compounds of formula XXXV above, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, are prepared by the hydrolysis of compounds of formula XXXVIII:-



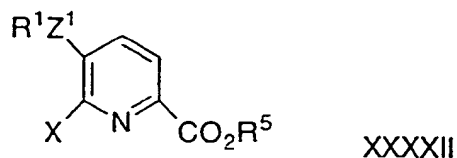
wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, e.g. by reaction with a base, such as an alkali metal carbonate or bicarbonate in the presence of water, followed by reaction with an aqueous acid such as dilute hydrochloric acid.

Compounds of formula XXXVIII above, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, can be prepared from compounds of formula XXXIX wherein R^1 , Q^1 , Q^2 , Q^3 and Z^1 are as herein before defined, by reaction



with compounds of the formula XXXVII, wherein R^2 is as hereinbefore defined, preferably in the presence of diisopropyl azodicarboxylate and triphenylphosphine.

Alternatively, compounds of formula VIIa, wherein Z^1 , R^1 , R^2 , and R^5 are as hereinbefore defined, and Q^1 and Q^2 are CH, and Q^3 is nitrogen, are prepared by reaction of compounds of formula XXXXII:-



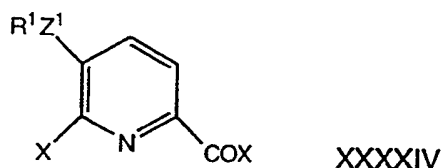
wherein X, Z^1 , R^1 and R^5 are as hereinbefore defined, with compounds of formula XXXXIII:-



wherein R^2 is as hereinbefore defined and M represents an alkali metal, e.g. sodium, atom, preferably in the presence of a base, for example alkali metal or alkali metal hydride, such as sodium or sodium hydride, without co-solvent or in the presence of an inert solvent, such as tetrahydrofuran, from about room temperature to reflux, preferably at about room temperature.

Compounds of formula XXXXII, wherein X, Z^1 , R^1 and R^5 are as hereinbefore defined, are prepared by the reaction of compounds of formula XXXXIV:-

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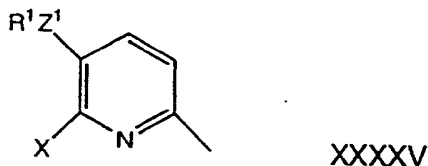
wherein X, Z^1 and R^1 are as hereinbefore defined, with compounds of formula XXXXV:-

15



wherein R^5 is as hereinbefore defined, preferably using the compound of formula XXXXV as the solvent, from about room temperature to reflux.

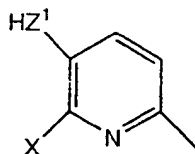
20 Compounds of formula XXXXIV, wherein X, R^1 and Z^1 are as hereinbefore defined, are prepared from compounds of formula XXX:-



25 wherein X, R^1 and Z^1 are as hereinbefore defined, by adaptation of procedures described by K.R.Reistad *et al.*, Acta. Chemica. Scandinavica B, 28, 667-72 (1974), incorporated herein by reference.

30 Compounds of formula XXXXV above, wherein X, R^1 and Z^1 are as hereinbefore defined, are prepared by the reaction of compounds of formula XXXXVI:-

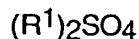
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XXXXVI

wherein X and Z¹ is as hereinbefore defined, with compounds of formula XXXXVII, wherein R¹ is as hereinbefore defined, by adaptation of

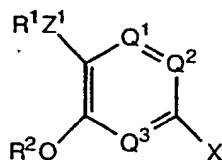
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XXXXVII

procedures described by K.R.Reistad *et al.*, Acta. Chemica. Scandanavica B, 28, 667-72 (1974), incorporated herein by reference.

- 10 Compounds of formula VI above, wherein R¹, R², R³, Q¹, Q², Q³ and Z¹ are as hereinbefore defined, are prepared by the reaction of compounds of formula XXXX wherein R¹, R², Q¹, Q², Q³ and Z¹ are as hereinbefore defined



XXXX

15

and X represents halo, e.g. bromo, with compounds of the formula XXXXI



wherein R³ is as hereinbefore defined, in the presence of a base such as butyl lithium, preferably at a low temperature.

- 20 Alternatively, compounds of formula VI above, wherein R¹, R², R³, Q¹, Q², Q³ and Z¹ are as hereinbefore defined, are prepared by the reaction of compounds of formula XVI above, wherein R¹, R², Q¹, Q², Q³ and Z¹ are as hereinbefore defined, with compounds of the formula VIII above, wherein R³ is as hereinbefore defined, in the presence of a base such as lithium
- 25 diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), preferably at a low temperature.

- For example, phenols and thiophenols of formula XIX above, wherein R¹, R³, Q¹, Q², Q³ and Z¹ are as hereinbefore defined, are prepared by the alkaline hydrolysis of their benzoyl esters, which themselves are prepared by
- 30 reaction of the benzoyl esters of the corresponding sulfonyl chlorides having reacted with compounds of formula III above, wherein R³ is as hereinbefore

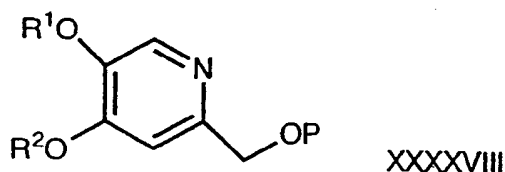
defined. The said sulfonyl chlorides are prepared by the action of thionyl chloride on the corresponding sulfonic acids, which themselves are prepared by insertion of the sulfo-group into the benzene ring by the action of chlorosulfonic acid.

5. Compounds of formula XXI, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, are prepared by the reaction of bromine in carbon tetrachloride and ultraviolet radiation on the corresponding $-CHF_2$ compounds, which themselves are prepared by the action of sulfur tetrafluoride and hydrofluoric acid on compounds of formula XVI above, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, in the presence of pyridine.

Compounds of formula XXIX above, wherein R^1 , R^2 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, are prepared by the reaction of selenium dioxide on the corresponding acetophenones in the presence of pyridine.

- 15 Compounds of formula XXXIV above, wherein R^1 , R^2 , R^3 , Q^1 , Q^2 , Q^3 and Z^1 are as hereinbefore defined, are prepared similarly by the reaction of the corresponding phenylacetaldehyde derivatives with compounds of formula XXXI above, wherein R^3 is as hereinbefore defined, in the presence of a base such as lithium diisopropylamide.

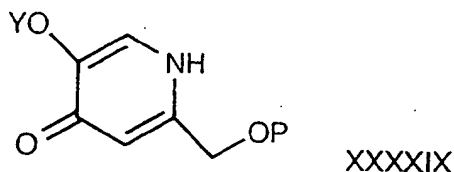
- 20 Compounds of formula XXVIII above, wherein Z^1 represents oxygen, Q^1 and Q^3 represent CH , and Q^2 represents a nitrogen atom, and R^1 and R^2 are as hereinbefore defined are prepared from compounds of formula XXXXVIII:-



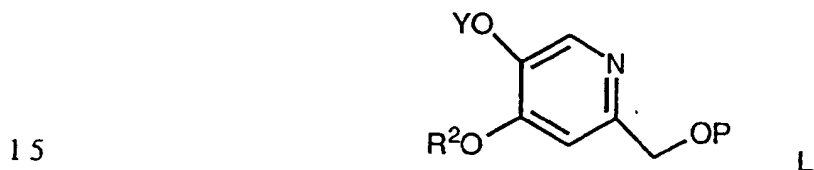
- 25 wherein R^1 and R^2 are as hereinbefore defined, and P represents a protecting group, such as a silyl group, for example *t*-butyldimethylsilyl, or a trityl group, by reaction with an excess or a catalytic quantity of aqueous acid, for example formic acid, trifluoroacetic acid or acetic acid, neat or in the presence of a co-solvent, for example ethyl acetate, at a temperature from about room temperature to about 100°C.

30 Compounds of formula XXXXVIII above, wherein R^1 , R^2 and P are as hereinbefore defined, are prepared by the reaction of compounds of formula XXXXIX:-

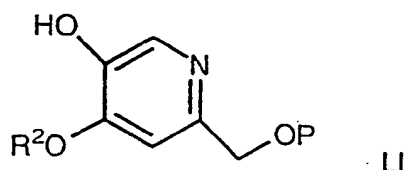
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- wherein Y represents P¹ or R¹, P¹ represents a protecting group, such as a benzyl group, and R¹ and P are as hereinbefore defined; (1) where Y of
 5 formula XXXXIX represents R¹, with compounds of formula XXXVII, wherein R² is as hereinbefore defined, in the presence of a dialkyl diazodicarboxylate, for example diisopropyl diazodicarboxylate, and a phosphine, preferably a triarylphosphine, such as triphenyl-phosphine, in an inert solvent, for example toluene or an ether, such as tetrahydrofuran or diethyl ether, at a temperature
 10 from about -20°C to reflux, or (2) where Y of formula XXXXIX represents P¹, a protecting group as hereinbefore defined, then a compound of formula XXXXIX is treated as in procedure (1) immediately hereinbefore described to prepare compounds of formula L:-



- wherein Y is P¹, and P, P¹ and R² are as herein before defined, that are then selectively deprotected to remove P¹ as a benzyl group, for example by hydrogenolysis in the presence of a supported metal catalyst, such as 5%
 20 palladium on charcoal, in an inert solvent, for example ethyl acetate, or preferably ethanol to yield compounds of formula LI:-

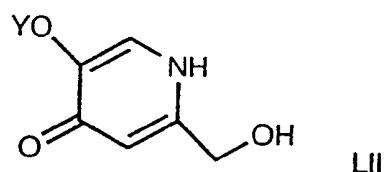


- 25 wherein P and R² are as hereinbefore defined, that are then alkylated with compounds of formula LI:-



wherein R¹ and X are hereinbefore defined, in the presence of a base, for example an amine, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, or preferably an alkali metal carbonate, such as potassium carbonate, in an inert solvent, for example dimethylformamide, at a temperature from about 0°C to about 120°C.

5. Compounds of formula XXXIX above, wherein Y and P are as hereinbefore defined, are prepared by the reaction of compounds of formula LII:-



10

wherein Y is as hereinbefore defined, with compounds of formula LIII:-

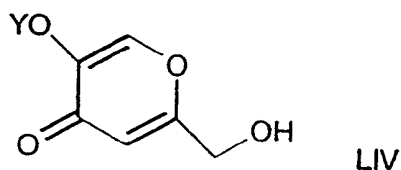


- wherein P and X are as hereinbefore defined, preferably in the presence of base, for example an amine, preferably a tertiary amine, for example triethylamine or preferably 4-dimethylaminopyridine, in an inert solvent, for example dimethylformamide or tetrahydrofuran, at from about room temperature to about 120°C, preferably from about 60°C to about 100°C.

15

Compounds of formula LII above, wherein Y is as hereinbefore defined, are prepared from compounds of formula LIV:-

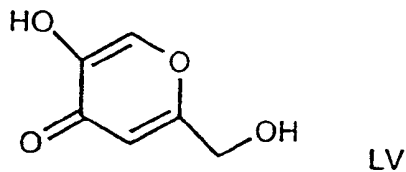
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- wherein Y is as hereinbefore defined, by adaptation of the procedures described by H.C.Beyerman, Receueil, 77, 249-57, (1958) and European Patent 204207 (20/05/86), incorporated herein by reference.

25

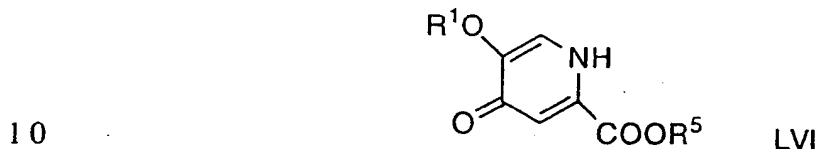
Compounds of formula LIV wherein Y is as hereinbefore defined, are prepared by the reaction of compounds of formula LV:-



with compounds of formula XXXVII above, wherein R^1 is as hereinbefore defined, by adaptation of the alkylation procedure described by H.C.Beyerman, Receueil, 77, 249-57, (1958) and European Patent 204207 (20/05/86),

5. incorporated herein by reference.

Compounds of formula VIIa, wherein Z^1 represents an oxygen atom, Q^1 and Q^3 represent CH, Q^2 represents N, and R^1 , R^2 and R^7 are as hereinbefore defined are prepared by the reaction of compounds of formula LVI:-

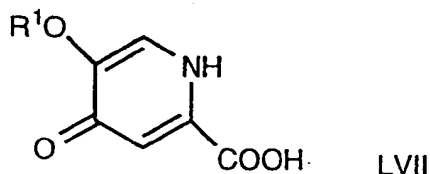


wherein R^1 and R^5 are as hereinbefore defined, with compounds of formula XXXVII above, wherein R^2 is as hereinbefore defined, in the presence of a dialkyl diazodicarboxylate, for example diisopropyl diazodicarboxylate, and a phosphine, preferably a triarylphosphine, such as triphenylphosphine, in an inert solvent, for example toluene or an ether, such as tetrahydrofuran or diethyl ether, at a temperature from about -20°C to reflux.

15

Compounds of formula LVI above, wherein R^1 and R^5 are as hereinbefore defined, are prepared by the reaction of compounds of formula LVII:-

20



wherein R^1 is as hereinbefore defined, with compounds of formula XXXXV, wherein R^5 is as hereinbefore defined, in the presence of an acid, preferably a mineral acid, for example sulphuric acid, or preferably hydrogen chloride, at a temperature from about 0°C to reflux, preferably at an elevated temperature.

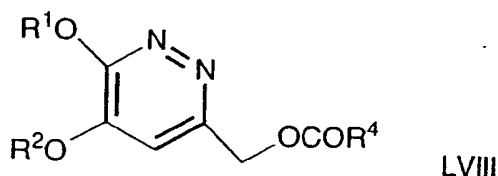
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Compounds of formula LVII above, wherein R^1 is as hereinbefore defined, are prepared from compounds of formula LII above, wherein Y is R^1 , and R^1 is as hereinbefore defined, by adaptation of the procedure described

30

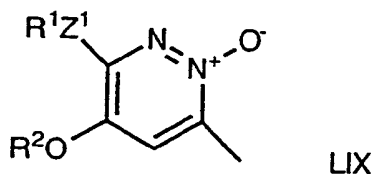
by H.C.Beyerman, Receueil, 77, 249-57, (1958), incorporated herein by reference.

Compounds of formula XXVIII above, wherein Q¹ and Q² are N, Q³ is CH, R¹ R² are as hereinbefore defined, and Z¹ represents an oxygen atom;
 5 are prepared from compounds of formula LVIII



wherein R¹, R², and R⁴ are as hereinbefore defined, by reaction with aqueous
 10 alkali metal hydroxide or carbonate, such as potassium hydroxide or preferably potassium carbonate, in an inert co-solvent, such as methanol, at a temperature from about room temperature to reflux.

Compounds of formula LVIII above, wherein R¹, R², and R⁴ are as
 15 hereinbefore defined, are prepared from compounds of formula LIX:-



wherein R¹ and R² are as hereinbefore defined (prepared by adaptation of the
 20 method of M.Ogata and H.Kano, J. Heterocyclic Chem., 11, 29-35, (1963), incorporated herein by reference), by reaction with compounds of the formula LX:-



wherein R⁴ is as hereinbefore defined, preferably a methyl group, using
 25 compound LX as solvent, at about room temperature to reflux, preferably at elevated temperature.

The present invention is further Exemplified but not limited by the following illustrative Examples which illustrate the preparation of the compounds according to the invention. The Reference Examples illustrate the preparation of the intermediates.

- 5 The oxaaliphatic groups attached to the 2-oxy moiety, in the compounds according to the invention are obtained from the corresponding hydroxy or halo substituted oxaaliphatic compounds. Aldrich® is an example of a source for hydroxy or halo substituted oxaaliphatic compounds such as 3-hydroxy-tetrahydrofuran, tetrahydro-4*H*-pyran-4-ol, tetrahydropyran-2-methanol, 10 tetrahydro-2*H*-2-methyl bromide, tetrahydro-3-furylmethanol, tetrahydrofuryl alcohol, tetrahydrofuryl chloride, 1-methoxy-2-propanol, 2-methoxyethanol, 2-methoxyethyl chloride, 3-methoxy-1-butanol, 2-isopropoxyethanol, 3-ethoxy-1-propanol, 2-ethoxyethanol, 4-chloro-tetrahydropyran, 2-chloroethylether, 2-butoxyethanol and 2-(2-butoxyethoxy)ethanol. Other hydroxy substituted 15 oxaaliphatic compounds that are used according to the invention and references for preparing them, incorporated herein by reference, include: 4-methoxy-3-methylbut-1-en-3-ol (J. Colonge et al., Bull. Soc. Chim. France, 619-25 (1965)), 2-(prop-2-yn-1-oxy)ethanol (U.S. Patent No. 3,048,598 issued August 7, 1962 to W. Croxall et al.), (3,4-dihydro-2*H*-pyran-6-yl)methanol 20 (A. Lebouc et al., Synthesis, 610-13 (1979)), (3,4-dihydro-2*H*-pyran-2-yl)methanol (C. Fehr et al., Helv. Chim. Acta, 64, 1247-56 (1981)), 7-oxabicyclo[2.2.1]-heptan-2-ol (P. Flury et al., Helv. Chim. Acta, 71, 1017-24 (1988)), 7-oxa-bicyclo[2.2.1]hept-5-en-ol (R. Saf et al., Tetrahedron, 44, 389-92 (1988)), *endo*-2-oxabicyclo[2.2.1]hept-6-ol (L. Spurlock et al., JACS, 94, 2707- 25 11 (1972)), *exo*-2-oxabicyclo[2.2.1]hept-6-ol L. Spurlock et al., *ibid.*) and (R. Saf et al., *ibid.*).

- In the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significance: s=singlet; d=doublet; t=triplet; m=multiplet; dd=doublet 30 of doublets; ddd=doublet of doublets of doublets; dt=doublet of triplets, b=broad.

EXAMPLE 1 Compounds A and B

- To a stirred solution of 3,5-dichloro-4-aminopyridine (1.63 g) in dry dimethylformamide (30 mL) was added portionwise a suspension of sodium 35 hydride (0.8 g of a 60% oil dispersion) over 15 minutes. To this solution was added dropwise a solution of 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride (2.7 g; prepared as in Reference Example 115) in dry

dimethylformamide (10 mL) and the solution stirred for 3 hours. Water (50 mL) was added and the solution concentrated to low bulk. Water (100 mL) was added and the mixture extracted with ethyl acetate (2 x 150 mL). The organic layers were combined, dried (MgSO₄) and concentrated to give an oil. The residue was purified by flash chromatography on silica gel, eluting with a mixture of ether and pentane (7:3 v/v), to give (2.4 g) of (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide m.p. 116-118°C. [Elemental analysis: C, 53.2; H, 4.2; Cl, 18.2; N, 7.4; calculated: C, 53.3; H, 4.2; Cl, 18.2; N, 7.4%].

By proceeding in a similar manner, but replacing 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride with 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoyl chloride (prepared as in Reference Example 51), there was prepared (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)benzamide as a colorless solid. m.p. 116-118°C (decomp.). [Elemental analysis: C, 54.4; H, 4.9; N, 6.6%; calculated: C, 54.4; H, 4.6; N, 7.0%].

EXAMPLE 2 Compound C

To a suspension of (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (1.5 g, which is prepared as in Example 1) in glacial acetic acid (20 mL) was added a solution of 30% w/w aqueous hydrogen peroxide (8 mL) and the solution heated at 80°C for 5 hours. After cooling, water (10 mL) was added and the solution evaporated to low bulk under reduced pressure. The residue was carefully basified with the minimum quantity of 6N NaOH solution and then neutralized to pH 7 with concentrated HCl. The solution was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried over MgSO₄ and concentrated to give a pale yellow solid. The solid was subjected to flash chromatography on silica gel, eluting with ethyl acetate and then methanol/ethyl acetate (1:9), to give 0.8 g (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide, m.p. 168-170°C. [Elemental analysis: C, 51.1; H, 4.1; Cl, 17.6; N, 6.9%; calculated: C, 51.15; H, 4.0; Cl, 17.8; N, 7.0%]

EXAMPLE 3 Compound D

Sodium hydride (0.34 g) was added portionwise to a stirred solution of 4-amino-3,5-dichloropyridine (0.7 g) in dry dimethylformamide (30 mL) and stirred at room temperature under an atmosphere of nitrogen for one hour. A solution of 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride (1.25 g), that was prepared as described hereinafter in Reference Example 43), in

- dry dimethylformamide was added dropwise and stirred at room temperature under nitrogen for 3 hours. The reaction mixture was poured onto water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with brine, dried with MgSO₄, evaporated under reduced pressure and purified by mpic, eluting with ether to give (±)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide as a white solid (0.86 g). m.p. 118-120°C. [Elemental analysis: C, 48.85; H, 3.39; N, 6.57; Cl, 16.78%; calculated: C, 48.7; H, 3.37; N, 6.68; Cl, 16.92%].

EXAMPLE 4 Compound E

- Hydrogen peroxide (27.5%, 3 mL) was added to a solution of (±)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide (0.5 g, that was prepared as in Example 3) in glacial acetic acid (10 mL) and stirred at 70°C for six hours. The reaction mixture was neutralized with ethyl acetate (2 x 50 mL). The combined extract was dried over magnesium sulfate, evaporated under reduced pressure and purified by mpic, eluting with ethyl acetate, to give (±)-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide (0.18 g) as a white solid. m.p. 169-171°C (decomp.). [Elemental analysis: C, 47.4; H, 3.44; N, 6.44; Cl, 16.08%; calculated: C, 46.91; H, 3.24; N, 6.44; Cl, 16.29%].

EXAMPLE 5 Compounds AF-BE

- A stirred solution of 2,6-difluoroaniline (1.52 g) and triethylamine (1.19 g) in dichloromethane (50 mL) at room temperature is treated dropwise with a solution of 3-cyclopentyloxy-4-methoxybenzoyl chloride (3.0 g), that is prepared as described hereinafter in Reference Example 3) in dichloromethane (50 mL). The solution is stirred and heated at reflux for 4 hours, then it is cooled, washed with water and dried over magnesium sulfate. The solution is concentrated and the resulting residue is recrystallized from ethyl acetate, to give N-(2,6-difluorophenyl)-3-cyclopentyloxy-4-methoxybenzamide (1.9 g), m.p. 158-160°C [NMR(CDCl₃): 1.55-1.7(m, 3H), 1.8-2.05(m, 5H), 3.93(s, 3H), 4.85(m, 1H), 6.9(d, 1H), 6.95-7.03(m, 2H), 7.2-7.3(m, 1H), 7.35(bs, 1H), 7.45(q, 1H), 7.53(d, 1H); Elemental analysis: C, 65.1; H, 5.6; F, 10.4; N, 4.2%; Calculated: C, 65.7; H, 5.5; F, 10.9; N, 4.0%].

- By proceeding in a similar manner, but replacing the 2,6-difluoroaniline by the appropriate quantities of the corresponding aniline derivatives, there are prepared:

- N-(2-chloro-6-fluorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 140-142°C [Elemental analysis: C,62.3; H,5.2; Cl,9.7; N,3.6%; Calculated: C,62.7; H,5.3; Cl,9.75; N,3.85%];
5. N-(2-trifluoromethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 127-129°C [Elemental analysis: C,63.4; H,5.5; F,13.3; N,3.3%; Calculated: C,63.3; H,5.3; F,15.0; N,3.7%];
- N-(2,4,6-trichlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 173°C [Elemental analysis: C,55.2; H,4.4; Cl,26.4; N,3.1; Calculated: C,55.0; H,4.4; Cl,25.6; N,3.4%];
- 10 N-(2,6-dibromophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 133°C [Elemental analysis: C,48.5; H,4.0; Br,33.9; N,2.85%; Calculated: C,48.6; H,4.1; Br,34.1; N,3.0%];
- N-(2-chloro-6-methylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 138-140°C [Elemental analysis: C,66.3; H,6.2; Cl,10.3; N,3.8%; Calculated: C,66.75; H,6.2; Cl,9.85; N,3.9%];
- 15 N-(2,6-dichlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 138-140°C [Elemental analysis: C,59.8; H,5.1; Cl,19.1; N, 3.3%; Calculated: C,60.0; H,5.0; Cl,18.65; N,3.7 %];
- N-(2-fluorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m. p. 137 °C [Elemental analysis: C,69. 3 ; H,6. 2; F,5. 7; N,4.0%; Calculated: C,69.3; H,6.1;F,5.8; N,4.25%];
- 20 N-phenyl-3-cyclopentyloxy-4-methoxybenzamide, m. p. 169-173 °C [Elemental analysis: - C, 73. 2 ; H,6. 7; N,4.2%; Calculated: C,73.3; H,6.8; N,4.5%];
- N-(2-methoxyphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 132-134°C [Elemental analysis: C,70.1; H,6.8; N,4.0%; Calculated: C,70.4; H,6.8; N,4.1%];
- 25 N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 122-124°C [Elemental analysis: C,65.8; H,5.8; Cl,10.5; N,3.9%; Calculated: C,66.0; H,5.8; Cl,10.25; N,4.05%];
- N-(3-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 110-112°C [Elemental analysis: C,65.9; H,6.5; Cl,9.8; N,3.7%; Calculated: C,66.0; H,5.8; Cl,10.25; N,4.05%];
- 30 N-(4-methoxyphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 182-184°C [Elemental analysis: C,68.7; H,6.6;N,3.8%;Calculated for C₂₀H₂₃NO₄:1/2H₂O: C,68.55; H,6.9;N,4.0%];
- 35 N-(2,6-dimethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 130-131°C [Elemental analysis: C,74.2; H,7.4; N,4.1%; Calculated: C,74.3; H,7.4; N,4.13%];

- N-(2-methylthiophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 128-130°C [Elemental analysis: C,67.6; H,6.5; N,3.9; S,8.9%; Calculated: C,67.2; H,6.5; N,3.9; S,9.0%];
- N-(2-bromophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 126-128°C
5 [Elemental analysis: C,58.2; H,5.1; Br,20.4; N,3.5%; Calculated: C,58.5; H,5.2; Br,20.5; N,3.6%];
- N-(2-methoxycarbonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 105-107°C [Elemental analysis: 68.4; H,6.35; N,3.7%; Calculated: 68.3;6.3; N,3.8%];
- 1 0 N-(2-aminosulfonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 248°C [Elemental analysis: C,58.0; H,5.5; N,6.9%; Calculated: C,58.45; H,5.7; N,7.2%];
- N-(2-benzoylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 106-107°C [Elemental analysis: C,75.5; H,6.3; N,3.3%; Calculated: C,75.2; H,6.1; N,3.4%];
- 1 5 N-(2-cyanophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 170-172°C [Elemental analysis: C,71.0; H,6.0; N,8.1%; Calculated: C,75.2; H,6.1; N,3.4%];
- N-(2,5-dichlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 117-119°C [Elemental analysis: C,59.7; H,5.0; Cl,18.5; N,3.7%; Calculated: C,60.0; H,5.0; Cl,18.65; N,3.7%];
- 2 0 N-(3-methylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 147-149°C [Elemental analysis: C,73.8; H,7.1; N,4.2%; Calculated: C,73.8; H,7.1; N,4.3%];
- N-(2-nitrophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 130-132°C [Elemental analysis: C,64.0; H,5.7; N,7.4%; Calculated: C,64.0; H,5.7; N,7.9%];
- N-(2-dimethylaminophenyl)-3-cyclopentyloxy-4-methoxybenzamide, in the
2 5 form of a brown oil [Elemental analysis: C,71.5; H,7.4; N,7.4%; Calculated: C,71.2; H,7.4; N,7.9%];
- N-(2-acetylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 126-127°C [Elemental analysis: C,71.0; H,6.6; N,3.9%; Calculated: C,71.4; H,6.6; N,4.0%]; and
- 3 0 N-(2-hydroxyphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 169-171°C [Elemental analysis: C,69.5; H,6.5; N,3.9%; Calculated: C,69.7; H,6.5; N,4.3%].
- By proceeding in a similar manner, but replacing 3-cyclopentyloxy-4-methoxybenzoyl chloride by 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, that is prepared as described hereinafter in Reference Example 3,
3 5 and using the appropriate quantities of the corresponding aniline derivatives, there are prepared:
- N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-(2-chloro-6-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-trifluoromethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,4,6-trichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dibromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 5 N-(2-chloro-6-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-phenyl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 10 N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(3-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dimethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-methylthiophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 15 N-(2-bromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-aminosulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-benzoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 20 N-(2,5-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(3-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-dimethylaminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2-acetylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
 25 N-(2-hydroxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 6 Compounds BF-BG

- A stirred solution of N-(2-methylthiophenyl)-3-cyclopentyloxy-4-methoxybenzamide (1.80 g; that is prepared as described hereinbefore in Example 5) is treated with a solution of 3-chloroperbenzoic acid (3.60 g; 85%
 30 pure) in dichloromethane (72 mL), dropwise, and then it is stirred at room temperature for 5 hours. The reaction mixture is washed with saturated aqueous sodium bicarbonate solution and then with water, and then it is dried over magnesium sulfate. The mixture is concentrated to give N-(2-methylsulfonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, (1.12 g), in the form of
 35 a white solid, m.p. 119-121°C [NMR(CDCl₃): 1.52-2.16 (m,8H), 3.1(s,3H), 3.94(s,3H), 4.9(m,1H), 6.96(d,1H), 7.46 (m,1H), 7.6(m,2H), 7.7(t,1H), 7.95(d,1H),

8.68(d, 1H); Elemental analysis: C, 61.6; H, 6.0; N, 3.5; S, 8.5%; Calculated: C, 61.7; H, 5.95; N, 3.6; S, 8.5%].

- 5 By proceeding in a similar manner, but replacing N-(2-methylthiophenyl)-3-cyclopentyloxy-4-methoxybenzamide by N-(2-methylthiophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide, that is prepared as described above in Example 5, there is prepared:

N-(2-methylsulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 7 Compounds BH-BM

- 10 By proceeding in a manner similar to that described hereinbefore in Example 5, but using the appropriate quantities of the corresponding acid chlorides, which are prepared as described hereinafter in Reference Example 3, there are prepared:

N-(2,6-difluorophenyl)-3-cyclohexyloxy-4-methoxybenzamide, m.p. 60°C

[Elemental analysis: C, 66.1; H, 6.3; N, 3.3%; Calculated: C, 66.5; H, 5.9; N, 3.9%];

- 15 N-(2,6-difluorophenyl)-3-butoxy-4-methoxybenzamide, m.p. 150-152°C.

[Elemental analysis: C, 64.6; H, 5.8; N, 4.2; Calculated: C, 64.5; H, 5.7; N, 4.2%];

N-(2,6-difluorophenyl)-3-propoxy-4-methoxybenzamide, m.p. 170-174°C.

[Elemental analysis: C, 63.4; H, 5.4; N, 4.4%; Calculated: C, 63.5; H, 5.3; N, 4.4%];

- 20 N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)benzamide;
N-(2,6-difluorophenyl)-3-(2-ethoxyethoxy)-4-methoxybenzamide; and
N-(2,6-difluorophenyl)-4-methoxy-3-(2-methoxyethoxy)benzamide.

EXAMPLE 8 Compounds BN-BO

- 3-Cyclopentyloxy-4-methoxybenzoyl chloride (13.3 g) and 2-chloroaniline (6.6 g) are dissolved in pyridine (50 mL) and the solution is
25 allowed to stand at room temperature for 1 hour. Phosphorus pentasulfide (13 g) is added and the stirred mixture is heated at 110°C for 1.5 hours. After cooling to room temperature the mixture is poured into an ice-cold solution of concentrated hydrochloric acid (100 mL) in water (400 mL). The mixture is stirred for 1 hour and the yellow solid is collected, washed with water and
30 subjected to flash chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (3:1 v/v), to give N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxy(thiobenzamide) (5.4 g), m.p. 129-131°C [Elemental analysis: C, 62.6; H, 5.5; N, 3.9; S, 8.9%; Calculated: C, 63.1; H, 5.6; N, 3.9; S, 8.9%].

- 35 By proceeding in a manner similar, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, which is prepared as described hereinafter in

Reference Example 115, instead of 3-cyclopentyloxy-4-methoxybenzoyl chloride, there is prepared:

N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide)

EXAMPLE 9 Compounds BP-CG

5. A stirred solution of 4-chloropyrid-3-ylamine (1.94 g) and 3-cyclopentyloxy-4-methoxybenzoyl chloride (3.85 g) in pyridine (50 mL) is heated at 80°C for 7 hours and then it is allowed to stand overnight. The reaction mixture is evaporated, to give a brown oil, which is subjected to mpc on silica gel, using diethyl ether as eluent, to give N-(4-chloropyrid-3-yl)-3-cyclopentyloxy-4-methoxybenzamide (3.1 g), m.p. 130-132°C.

By proceeding in a similar manner, but using the appropriate quantities of the appropriate amines instead of the 4-chloropyrid-3-ylamine used as a starting material, there are prepared:

- N-pyrid-2-yl-3-cyclopentyloxy-4-methoxybenzamide, m.p. 92-94°C;
1 5 N-pyrazin-2-yl-3-cyclopentyloxy-4-methoxybenzamide, m.p. 80-82°C;
N-pyrimidin-2-yl-3-cyclopentyloxy-4-methoxybenzamide, m.p. 108-110°C;
N-(3-methylpyrid-2-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 55°C;
N-pyrid-3-yl-3-cyclopentyloxy-4-methoxybenzamide, m.p. 170-172°C;
N-(3-chloropyrid-2-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 138-
2 0 140°C;
N-(3-chloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 124-126°C;
N-pyrid-4-yl-3-cyclopentyloxy-4-methoxybenzamide, m.p. 163-165°C;
N-(4-chloropyrid-3-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
2 5 N-pyrid-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-pyrazin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-pyrimidin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-(3-methylpyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-pyrid-3-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
3 0 N-(3-chloropyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-(3-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
N-pyrid-4-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 10 Compounds CH and A

- 4-Amino-3,5-dichloropyridine (4.0 g) and 3-cyclopentyloxy-4-methoxybenzoyl chloride (6.26 g) are intimately ground together in a mortar with a pestle, and transferred to a round-bottomed flask. The mixture is melted, using a hot air gun external to the flask, stirring with a magnetic stirrer. After 10

minutes, heating is ceased and the melt is allowed to cool. The resulting material is triturated with dichloromethane and the residual solid is filtered off. The filtrate is concentrated to give a fawn solid, which is subjected to flash chromatography on silica gel, eluting with diethyl ether, to give N-(3,5-dichloro-
5 pyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (1.87 g), m.p. 155-157°C. [Elemental analysis: C,56.3; H,4.7; N,7.2; Cl,18.4%; calculated: C,56.7; H,4.76; N,7.35; Cl,18.6%; IR spectrum: 1661 cm⁻¹, 3244 cm⁻¹]

By proceeding in a manner similar, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, which is prepared as described hereinafter in
10 Reference Example 115, instead of 3-cyclopentyloxy-4-methoxybenzoyl chloride, there is prepared:

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

Alternatively, a suspension of 3-cyclopentyloxy-4-methoxybenzamide (2.58 g; that is prepared as described in Reference Example 73) in dry toluene
15 (40 mL) is heated at reflux and treated with potassium t-butoxide (1.4 g), followed by 3,4,5-trichloro-pyridine (1.82 g). The mixture is then heated at reflux for 3 hours and 45 minutes, and is then treated with a further quantity of potassium t-butoxide (1.4 g) and heated at reflux for a further period of 7 hours. The mixture is allowed to cool and is then filtered. The filtrate is evaporated
20 and the resulting residue is extracted with aqueous sodium hydroxide solution (2 M). The alkaline solution is then acidified by treatment with acetic acid, and the solid which separates is collected by filtration, washed with water and dried, to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (2.09 g) in the form of a buff solid, m.p. 153-155°C.

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzamide, which is prepared as described hereinafter in Reference Example 73, instead of 3-cyclopentyloxy-4-methoxybenzamide, there is prepared:

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

30 EXAMPLE 11 Compounds CI-CJ

By proceeding in a manner similar to that described hereinbefore in Example 5, but replacing the 2,6-difluoroaniline that is used as a starting material by the appropriate quantity of 4-amino-3,5-dimethylisoxazole, there is prepared N-(3,5-dimethylisoxazol-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 150-152°C. [Elemental analysis: C,65.6; H,6.8; N,8.5%;
35 calculated: C,65.4; H,6.7; N,8.5%11].

- By proceeding in a manner similar, but replacing the 2,6-difluoroaniline that is used as a starting material by the appropriate quantity of 4-amino-3,5-dimethylisoxazole and using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, which is prepared as described hereinafter in Reference Example 5, instead of 3-cyclopentyloxy-4-methoxybenzoyl chloride, there is prepared N-(3,5-dimethylisoxazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 12 Compounds CI, CK-DY

- By proceeding in a similar manner to that described hereinbefore in Example 5, but using the appropriate quantities of the corresponding benzoyl halides and amines as starting materials, and using dimethylformamide or tetrahydrofuran as the reaction solvent, there are prepared:
- N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (7.0 g).
N-(3,5-dichloropyrid-4-yl)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 149-150°C [Elemental analysis: C,58.8; H,4.9; N,6.7%; calculated: C,59.0; H,5.0; N,6.9%];
- N-(3,5-dichloropyrid-4-yl)-3-cyclohexyloxy-4-methoxybenzamide, m.p. 170°C [Elemental analysis: C,57.8; H,5.1; N,7.0; Cl,17.8%; calculated: C,57.7; H,5.1; N,7.1; Cl,17.9%];
- N-(3,5-dibromopyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 160-162°C [Elemental analysis: C,46.4; H,3.9; N,6.1%; calculated: C,46.0; H,3.9; N,6.0%];
- N-(3,5-dichloropyrid-4-yl)-3-butoxy-4-methoxybenzamide, m.p. 165-167°C [Elemental analysis: C,55.1; H,4.8; N,7.6; Cl,19.2%; calculated: C,55.3; H,4.9; N,7.6; Cl,19.2%];
- N-(3,5-dimethylpyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 77-80°C [Elemental analysis: C,67.2; H,6.9; N,7.8%; calculated: C,67.0; H,7.3; N,7.8%];
- N-(2,6-dichloro-4-cyanophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 170-172°C [Elemental analysis: C,59.1; H,4.5; N,7.0; Cl,17.5%; calculated: C,59.3; H,4.5; N,6.9; Cl,17.5%];
- N-(2,6-dichloro-4-methoxycarbonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 158-160°C [Elemental analysis: C,57.4; H,4.9; N,3.2; Cl,16.4%; calculated: C,57.5; H,4.8; N,3.2; Cl,16.2%];
- N-(2,3,5-trifluoropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 144-146°C [Elemental analysis: C,59.3; H,4.9; N,7.5%; calculated: C,59.0; H,4.7; N,7.65%];

- N-(2,6-dichloro-4-ethoxycarbonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 164-166°C;
- (R)-N-(3,5-dichloropyrid-4-yl)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 155-156°C [Elemental analysis: C,58.8; H,5.0; N,6.8%];
- 5 (S)-N-(3,5-dichloropyrid-4-yl)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 156-157°C;
- N-(2,6-dichloro-4-nitrophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 154-156°C;
- 10 3-cyclopentyloxy-N-(3,5-difluoropyrid-4-yl)-4-methoxybenzamide, m.p. 160-161°C. [Elemental analysis: C,61.7; H,5.2; N,8.0%; calculated: C,62.1; H,5.2; N,8.0%];
- (R)-N-(2,6-dichlorophenyl)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 144-145°C. [Elemental analysis: C,61.7; H,5.1; N,3.3%;
- 15 calculated: C,62.1; H,5.2; N,3.45%];
- (S)-N-(2,6-dichlorophenyl)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 143-144°C. [Elemental analysis: C,62.1; H,5.2; N,3.1%; calculated: C,62.1; H,5.2; N,3.45%];
- 3-cyclopentylmethoxy-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide, m.p.
- 20 192-200°C. [Elemental analysis: C,58.1; H,5.1; N,7.1%; calculated: C,57.7; H,5.1; N,7.1%];
- 3-cyclopropylmethoxy-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide, m.p. 226-230°C. [Elemental analysis: C,55.3; H,4.4; N,7.4%; calculated: C,55.6; H,4.4; N,7.6%];
- 25 N-(3-bromo-5-chloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 132-134°C. [Elemental analysis: C,50.8; H,4.2; N,6.5%; calculated: C,50.8; H,4.3; N,6.6%];
- N-(3,5-dichloropyrid-4-yl)-3-isopropoxy-4-methoxybenzamide, m.p. 175-176°C. [Elemental analysis: C,54.3; H,4.6; N,8.0%; calculated: C,54.1; H,4.5;
- 30 N,7.9%];
- 3-tert-butoxy-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide, m.p. 148-150°C. [Elemental analysis: C,55.3; H,4.95; N,7.5%; calculated: C,55.3; H,4.9; N,7.6%];
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(pent-3-oxy)benzamide, m.p. 133-
- 35 134°C. [Elemental analysis: C,56.5; H,5.25; N,7.3; Cl,18.4%; calculated: C,56.4; H,5.26; N,7.3; Cl,18.5%];
- 3-[2-(2-butoxyethoxy)ethoxy]-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide;

- N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(3,5-dichloropyrid-4-yl)-3-(2-ethoxyethoxy)-4-methoxybenzamide;
 N-(3,5-dimethylpyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dichloro-4-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-
 5 benzamide;
 N-(2,6-dichloro-4-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,3,5-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dichloro-4-ethoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 10 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
 15 N-(2,6-dichloro-4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(3,5-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 N-(2,6-dichlorophenyl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
 N-(2,6-dichlorophenyl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
 20 N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-methoxybenzamide;
 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-2H-pyran-2-oxymethyl)benzamide;
 N-(3-bromo-5-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
 25 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxy-2-propoxy)benzamide;
 N-(3,5-dichloropyrid-4-yl)-3-(2-isopropoxyethoxy)-4-methoxybenzamide; and
 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(3-methoxy-1-butoxy)benzamide.

EXAMPLE 13 Compound DZ

- A stirred suspension of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (2.0 g; that is prepared as described in Example 10) in
 30 glacial acetic acid (8 mL) is treated with an aqueous solution of hydrogen peroxide (6 mL; 27.5%). The mixture is stirred for 3 hours at 70-80°C and then it is treated with a further portion of hydrogen peroxide solution (4 mL), and the solution is stirred for a further 12 hours. The solution is then cooled, basified by
 35 treatment with concentrated aqueous sodium hydroxide solution, and extracted with dichloromethane (2 x 30 mL). The organic extract is washed with brine (30 mL), dried over magnesium sulfate and evaporated. The resulting residue

is recrystallized from ethyl acetate, to give 3,5-dichloro-4-(3-cyclopentyloxy-4-methoxybenzamido)pyridine-N-oxide (0.73 g), m.p. 118-120°C [Elemental analysis: C,53.0; H,4.4; N,6.8%; calculated for $C_{18}H_{18}O_4N_2Cl_2 \cdot 0.5H_2O$: C,53.2; H 4.7; N 6.9%].

5. EXAMPLE 14 Compounds EA-EB.

A stirred solution of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (2.0 g; that is prepared as described in Example 6) in toluene (50 mL) is treated with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (3.0 g), and the mixture is heated at 100°C for 2
10 hours. After cooling to room temperature and filtration, the filtrate is concentrated in vacuo, to give a yellow oil. This oil is subjected to flash chromatography on silica gel, using a mixture of pentane and ethyl acetate (8:2 v/v) as eluent, to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxy(thiobenzamide) (0.64 g) m.p. 118-119°C [Elemental analysis: C,54.1;
15 H,4.6; Cl,17.4; N,6.8%; calculated: C,54.4; H,4.6; Cl,17.85; N,7.05%].

By proceeding in a manner similar, but replacing the N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide that is used as a starting material by the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide, which is prepared as described
20 hereinafter in Reference Example 1, there is prepared N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide).

EXAMPLE 15 Compounds EC-ED

A solution of N-(2,6-dichloro-4-nitrophenyl)-3-cyclopentyloxy-4-methoxybenzamide (1.5 g; that is prepared as described in Example 12) in
25 glacial acetic acid (22 mL) is treated with iron pin dust (1.3 g) and the mixture is heated with stirring at 90°C for 1 hour. The reaction mixture is cooled, basified to pH 8 by treatment with saturated aqueous sodium carbonate solution, and extracted with ethyl acetate (2 x 150 mL). The combined organic extract is dried over magnesium sulfate and concentrated in vacuo, to give a white solid.
30 This solid is subjected to flash chromatography, eluting with a mixture of ethyl acetate and pentane (1:1 v/v), to give N-(2,6-dichloro-4-aminophenyl)-3-cyclopentyloxy-4-methoxybenzamide (0.8 g), m.p. 170-172°C [Elemental analysis: C,54.8; H,5.04; N,6.5; Cl,17.4%; calculated: C,57.7; H,5.1; N,7.1; Cl,17.9%].

35 By proceeding in a manner similar, but replacing the N-(2,6-dichloro-4-nitrophenyl)-3-cyclopentyloxy-4-methoxybenzamide by the appropriate quantity of N-(2,6-dichloro-4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-

benzamide, which is prepared as described hereinafter in Reference Example 12, there is prepared N-(2,6-dichloro-4-aminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 16 Compounds EE-EF

5 Acetic anhydride (10 mL) is treated with N-(2,6-dichloro-4-aminophenyl)-3-cyclopentyloxy-4-methoxybenzamide (0.8 g; that is prepared as described in Example 15, and the reaction mixture is stirred for 2 hours and left to stand overnight. It is then poured into water (100 mL), and extracted with ethyl acetate (100 mL) and then with dichloromethane (100 mL). The organic
10 extracts are combined, dried over magnesium sulfate, and evaporated, to give N-(4-acetylamino-2,6-dichlorophenyl)-3-cyclopentyloxy-4-methoxybenzamide (0.4 g), m.p. 250-252°C [Elemental analysis: C,57.6; H,5.05; N,6.3; Cl,16.1%; calculated: C,57.5; H,5.1; N,6.4; Cl,16.2%].

By proceeding in a manner similar, but replacing the N-(2,6-dichloro-4-aminophenyl)-3-cyclopentyloxy-4-methoxybenzamide by the appropriate
15 quantity of N-(2,6-dichloro-4-aminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide, which is prepared as described hereinafter in Reference Example 15, there is prepared N-(2,6-dichloro-4-acetylamino-phenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

20 EXAMPLE 17 Compounds EG-EH and BL-BM

A stirred solution of N-(3,5-dichloropyrid-4-yl)-3-hydroxy-4-methoxybenzamide (2.0 g; that is prepared as described in Reference Example 12) in dimethylformamide (20 mL) at room temperature under nitrogen is treated portionwise with a suspension of sodium hydride (60%
25 dispersion in oil; 0.26 g), and then it is stirred for a further hour at room temperature. It is then treated dropwise with 1-bromononane (1.2 mL) and stirred at 60°C for 5 hours. The solution is then cooled to room temperature, diluted with water (60 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are dried over magnesium sulfate and evaporated,
30 to give a white solid, which is subjected to flash chromatography on silica gel, eluting with t-butyl methyl ether, to give N-(3,5-dichloropyrid-4-yl)-3-nonyloxy-4-methoxybenzamide (0.56 g), m.p. 151-153°C [Elemental analysis: C,60.3; H,6.45; N,6.3%; calculated: C,60.1; H,6.4; N,6.4%].

By proceeding in a similar manner, but using the appropriate quantity of
35 1-bromododecane there is prepared:
N-(3,5-dichloropyrid-4-yl)-3-dodecyloxy-4-methoxybenzamide, m.p. 143-145°C.

By proceeding in a similar manner, but using the appropriate quantity of 2-chloroethylether and 2-methoxyethyl chloride instead of 1-bromononane, and using N-(2,6-difluorophenyl)-3-hydroxy-4-methoxybenzamide (that is prepared as described in Reference Example 12) instead of N-(3,5-dichloropyrid-4-yl)-3-hydroxy-4-methoxybenzamide, there are prepared: N-(2,6-difluorophenyl)-3-(2-ethoxyethoxy)-4-methoxybenzamide; and N-(2,6-difluorophenyl)-4-methoxy-3-(2-methoxyethoxy)benzamide.

EXAMPLE 18 Compounds EI-EJ

A solution of N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide (4.4 g; that is prepared as described in Example 19) in dichloromethane (30 mL) is treated with activated manganese dioxide (6.2 g), and the mixture is stirred at reflux for 24 hours. The mixture is filtered, the filtrate is evaporated, and the resulting residue is subjected to flash chromatography on silica gel, eluting with ethyl acetate, to give N-(2,6-dichloro-4-formylphenyl)-3-cyclopentyloxy-4-methoxybenzamide (2.4 g), m.p. 96-98°C [Elemental analysis: C,59.0; H,5.1; N,3.1%; calculated: C,58.8; H,4.7; N,3.4%].

By proceeding in a similar manner, but using the appropriate quantity of N-(2,6-dichloro-4-hydroxymethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (that is prepared as described in Example 19) instead of N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, there is prepared N-(2,6-dichloro-4-formylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 19 Compounds EK-EL

A stirred solution of N-(2,6-dichloro-4-ethoxycarbonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide (6.1 g; that is prepared as described in Example 12) in dry tetrahydrofuran (80 mL) at room temperature under argon is treated dropwise with a solution of lithium borohydride in tetrahydrofuran (115 mL; 2 M). The mixture is stirred overnight and then it is treated portionwise with saturated brine (200 mL) and stirred for 30 minutes. The organic layer is then washed with water, dried over magnesium sulfate and evaporated. The resulting residue is subjected to flash chromatography on silica gel, to give N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide (4.4 g), m.p. 174-176°C [Elemental analysis: C,57.1; H,5.4; N,2.9%; calculated C₂₀H₂₁O₄NCI₂·0.5H₂O: C,57.3; H,5.3; N,3.3%]

By proceeding in a similar manner, but using the appropriate quantity of N-(2,6-dichloro-4-ethoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (that is prepared as described in Example 12) instead of N-(2,6-

dichloro-4-ethoxycarbonylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, there is prepared N-(2,6-dichloro-4-hydroxymethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 20 Compounds EM-EN

- 5 A solution of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (3.8 g; that is prepared as described in Example 10) in dry tetrahydrofuran (25 mL) is treated with a suspension of sodium hydride (60% dispersion in oil; 0.40 g), and the mixture is stirred until effervescence has ceased and a solution has formed. This solution is evaporated in vacuo and the resulting residue is triturated with t-butyl methyl ether (20 mL). The resulting off-white solid is filtered off, quickly washed with t-butyl methyl ether (2 x 20 mL) and dried, to give the sodium salt of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide (3.5 g), m.p. 265-270°C (with decomposition) [NMR(DMSO-D₆): 1.52-1.93(m,8H),4.77(s,3H),4.75-4.80 (m,1H),6.98(d,1H),7.58(dd,1H),7.60(s,1H),8.20(s,2H); IR spectrum: strong peak at 1508 cm⁻¹, with no peaks at or near 1661 cm⁻¹ nor 3244 cm⁻¹, which would have been characteristics of the starting material].

- By proceeding in a similar manner, but using the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (that is described as in Example 1) instead of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, there is prepared sodium salt of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 21 Compounds EO-ET

- By proceeding in a manner similar to that described in Example 9, but replacing the 4-chloropyrid-3-ylamine that is used as a starting material by the appropriate quantities of the corresponding aniline derivatives and using 3-cyclopentyloxy-4-methoxybenzoyl chloride and 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, there are prepared:

- N-(2,4,6-trifluorophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 160-162°C [Elemental analysis: C,62.5; H,5.0; N,3.6%; calculated: C,62.5; H,5.0; N,3.8%];
N-(2,6-dichloro-4-methoxyphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 126-128°C [Elemental analysis: C,57.9; H,4.9; N,3.2%; calculated: C,58.5; H,5.2; N,3.4%].
N-(2,4,6-trifluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
N-(2,6-dichloro-4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

By again proceeding in a similar manner, but replacing the 4-chloropyrid-3-ylamine and the 3-cyclopentyloxy-4-methoxybenzoyl chloride by the appropriate quantities of 2,6-dichloroaniline and 3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzoyl chloride (that is prepared as described in Reference Example 14) or 4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoyl chloride, there are prepared:

- N-(2,6-dichlorophenyl)-3-(~~exo~~-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzamide, m.p. 106-107°C [Elemental analysis: C,61.8; H,5.2; N,3.2%; calculated: C,62.1; H,5.2; N,3.45%]; and
- 10 N-(2,6-dichlorophenyl)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide

EXAMPLE 22 Compounds EU-FH

- By proceeding in a manner similar to that described in Example 10, but replacing the 4-amino-3,5-dichloropyridine that is used as a starting material
- 15 by the appropriate quantities of the corresponding amines and using 3-cyclopentyloxy-4-methoxybenzoyl chloride and 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride, there are prepared:

- N-(4,6-dichloropyrimid-5-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 191-193°C [Elemental analysis: C,53.1; H,4.4; Cl,18.6; N,10.9%; calculated: C,53.1; H,4.5; Cl,18.6; N,10.8%];
- 20 N-(2,3,5,6-tetrafluoropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 178-180°C [Elemental analysis: C,56.0; H,4.1; N,7.2%; calculated: C,56.25; H,4.2; N,7.3%];
- N-(3,5-dichloro-2,6-difluoropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 188-190°C [Elemental analysis: C,51.5; H,3.8; N,6.8; Cl,17.0%; calculated: C,51.8; H,3.9; N,6.7; Cl,17.0%];
- 25 N-(5-cyano-3-methylisothiazol-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 163-164°C [Elemental analysis: C,60.0; H,5.3; N,11.7%; calculated: C,60.5; H,5.85; N,11.8%];
- 30 N-(2,6-dichloro-4-carbamoylphenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 245-247° [Elemental analysis: C,54.0; H,4.5; N,6.4%; calculated: C,54.4; H,5.0; N,6.35%];
- N-(3-chloro-2,5,6-trifluoropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 188-190°C [Elemental analysis: C,53.7; H,3.95; N,6.81; Cl,8.9%; calculated: C,53.94; H,4.0; N,7.0; Cl,8.85%];
- 35 N-(4,6-dichloropyrimid-5-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-(2,3,5,6-tetrafluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
N-(3,5-dichloro-2,6-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
5 N-(5-cyano-3-methylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
N-(2,6-dichloro-4-carbamoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide; and
N-(3-chloro-2,5,6-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-
10 benzamide.

- By again proceeding in a similar manner, but replacing the 4-amino-3,5-dichloropyridine and the 3-cyclopentyloxy-4-methoxybenzoyl chloride by the appropriate quantities of 4-amino-3,5-dibromopyridine and 3-butoxy-4-methoxybenzoyl chloride and 4-methoxy-3-(2-ethoxyethoxy)benzoyl chloride
15 (that are prepared as described in Reference Example 3), there are prepared:
N-(3,5-dibromopyrid-4-yl)-3-butoxy-4-methoxybenzamide, m.p. 160-162°C [Elemental analysis: C,44.6; H,3.9; N,6.1%; calculated: C,44.6; H,4.0; N,6.1%];
and
N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(2-ethoxyethoxy)benzamide.

20 EXAMPLE 23 Compounds FI-FN

- By proceeding in a manner similar to that described in Example 5, but replacing the 2,6-difluoroaniline that is used as starting material by the appropriate quantities of the corresponding amines or using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride with the amines, there are prepared:
25 N-(4-nitrophenyl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 178-180°C [Elemental analysis: C,64.1; H,5.7; N,7.5%; calculated: C,64.0; H,5.7; N,7.9%];
N-(3-methyl-5-bromoisothiazol-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 160-162°C [Elemental analysis: C,50.0; H,4.7; N,6.8%; calculated: C,49.6; H,4.7; N,6.8%];
30 N-(3,5-dimethylisothiazol-4-yl)-3-cyclopentyloxy-4-methoxybenzamide, m.p. 140-141°C [Elemental analysis: C,62.4; H,6.35; N,8.0%; calculated: C,62.4; H,6.4; N,8.1%];
N-(4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
N-(3-methyl-5-bromoisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
35 N-(3,5-dimethylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.
EXAMPLE 24 Compounds FO-FP

A solution of 4-amino-3,5-dichloropyridine (0.46 g) in dry dimethylformamide (20 mL) is treated with sodium hydride (0.23 g of a 60% dispersion in mineral oil; 2.8 mmol) and the mixture is stirred for 20 minutes. It is then treated with a solution of 3-cyclopentyloxy-4-(methylthio)benzoyl chloride (0.76 g; that is prepared as described in Reference Example 20 in dimethylformamide (10 mL) and stirred at 60°C for 2 hours. The solution is then concentrated and the resulting residue is partitioned between water (30 mL) and ethyl acetate (50 mL). The aqueous layer is extracted with ethyl acetate (50 mL) and the combined organic layers are dried, concentrated, and subjected to flash chromatography on silica gel, eluting with a mixture of diethyl ether and pentane (1:1 v/v), to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(methylthio)benzamide (0.7 g) in the form of a white crystalline solid, m.p. 157-159°C [NMR (CDCl₃): 8.57 (s, 2H), 7.69 (bs, 1H), 7.47 (dd, 1H, J=8Hz, J=2Hz), 7.43 (d, 1H, J=2Hz), 7.17 (d, 1H, J=8Hz), 4.95 (m, 1H), 2.46 (s, 3H), 1.98-1.6 (m, 8H); Elemental analysis: C, 54.0; H, 4.5; N, 7.0; Cl, 17.8%; calculated: C, 54.4; H, 4.6; N, 7.05; Cl, 17.85%].

By proceeding in a manner similar, but replacing 3-cyclopentyloxy-4-(methylthio)benzoyl chloride by 4-(methylthio)-3-(tetrahydro-3-furyloxy)-benzoyl chloride (that is prepared as described in Reference Example 115), there is prepared: N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 25 Compounds FQ-FR

By proceeding as in Example 24 but using 4-amino-3,5-difluoropyridine instead of 4-amino-3,5-dichloropyridine, and using 3-cyclopentyloxy-4-(methylthio)benzoyl chloride and 4-(methylthio)-3-(tetrahydro-3-furyloxy)benzoyl chloride, there are prepared: N-(3,5-difluoropyrid-4-yl)-3-cyclopentyloxy-4-(methylthio)benzamide is synthesized; m.p. 174-5°C. [Elemental analysis: C, 59.4; H, 5.1; N, 7.6; S, 8.3%; calculated: C, 59.3; H, 5.0; N, 7.7; S, 8.3%]; and

N-(3,5-difluoropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 26 Compounds FS-FX

A solution of 4-amino-3,5-dichloropyridine (1.6 g) in dry tetrahydrofuran (20 mL) at 0°C under nitrogen is treated with sodium hydride (1 g of a 60% dispersion in mineral oil) and then stirred for a further 30 minutes at this temperature. It is then treated with a solution of 3-(*exo*)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride (2.8 g, that is prepared as described in Reference Example 23) in dry tetrahydrofuran (20 mL) keeping the

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temperature below 10°C. The resulting mixture is further stirred in the cold for 1 hour, allowed to warm to room temperature and left to stand overnight. The mixture is then quenched with 10% aqueous ammonium chloride solution (150 mL), the layers separated and the aqueous layer further extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are dried (Na₂SO₄) and evaporated to dryness. The resulting residue is subjected to flash chromatography on silica gel, eluting with ethyl acetate/pentane (gradient elution 1:4 v/v to 1:1 v/v) to give N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzamide (2.0 g) as an off white solid, m.p. 175-177°C (from isopropanol). [Elemental analysis: C,56.7; H,4.8; N,6.6%; calculated: C,56.7; H,4.8; N,6.6%].

By proceeding in a similar manner, but replacing the 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride that is used as a starting material by the appropriate benzoyl chloride derivatives (that are prepared as described in Reference Example 115) there are prepared:

(R)-N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzamide, m.p. 185-186°C (from ethyl acetate/t-butylmethyl ether), $[\alpha]_D^{21}$ -19.5° (c=0.91, CH₂Cl₂). [Elemental analysis: C,56.6; H,4.9; N,6.6%; Calculated: C,56.7; H,4.8; N,6.6%]; and

(S)-N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzamide, m.p. 188-189°C (from ethyl acetate/heptane) $[\alpha]_D^{20}$ +15.6° (c=1.24, CH₂Cl₂). [Elemental analysis: C,57.0; H,4.9; N,6.7%; Calculated: C,56.7; H,4.8; N,6.6%].

By also proceeding in a similar manner, but replacing the 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride by 4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoyl chloride, 4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzoyl chloride and 4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzoyl chloride (that are prepared as described in Reference Example 115) there are prepared:

N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;

N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide; and

N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide.

EXAMPLE 27 Compounds FZ-GA

A solution of 4-amino-3,5-dichloropyridine (3.73 g) in dry tetrahydrofuran (50 mL) under nitrogen at 5-10°C is treated portionwise with sodium hydride (60% dispersion in oil; 1.87 g). After 30 minutes it is treated dropwise with a solution of 3-cyclopent-2-enyloxy-4-methoxybenzoyl chloride in dry
5 tetrahydrofuran (50 mL; that is prepared, as described in Reference Example 32, from 5.89 g 3-cyclopent-2-enyloxy-4-methoxybenzoic acid). The resulting mixture is allowed to warm to room temperature and left to stand overnight. Most of the solvent is then removed under reduced pressure and the residue is partitioned between water (250 mL) and dichloromethane (250 mL) and the
10 aqueous layer is further extracted with dichloromethane (2 x 250 mL). The combined organic layers are dried over sodium sulfate, the solvent is removed under reduced pressure, and the resulting residue is subjected to flash chromatography on silica gel, eluting with mixtures of ethyl acetate and pentane (3:7 to 1:1 v/v), to give a cream solid (1.25 g), which is recrystallized
15 from a mixture of ethyl acetate and pentane, to give (±)-N-(3,5-dichloropyrid-4-yl)-3-cyclopent-2-enyloxy-4-methoxybenzamide (0.80 g), as a white solid, m.p. 177-178°C. [Elemental analysis: C,56.9; H,4.2; N,7.4; Cl,18.6%; calculated: C,57.0; H,4.3; N,7.4; Cl,18.7%].

By proceeding in a similar manner, but using 3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzoyl chloride (that is prepared, as described in
20 Reference Example 115, from 3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzoic acid) in dry tetrahydrofuran instead of 3-cyclopent-2-enyloxy-4-methoxybenzoyl chloride, there is prepared N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzamide.

25 EXAMPLE 28 compound GA-GB

A solution of 4-amino-3,5-dichloropyridine (0.93 g) in dry tetrahydrofuran (56 mL) under nitrogen at 5-10°C is treated portionwise with sodium hydride (60% dispersion in oil, 0.57 g). After 1 hour it is treated dropwise with a
30 solution of 3-cyclopent-3-enyloxy-4-methoxybenzoyl chloride in dry tetrahydrofuran (30 mL) that is prepared as described in Reference Example 32 from 1.33 g 3-cyclopent-3-enyloxy-4-methoxybenzoic acid. The resulting mixture is allowed to warm to room temperature, stirred for a further 3 hours and then poured into 5% aqueous potassium carbonate (430 mL). The
35 resulting emulsion is extracted with ethyl acetate (3 x 150 mL), the combined organic extracts washed with water (2x20 mL), followed by ice-cold 1 M aqueous hydrochloric acid (2 x 20 mL) and dried over sodium sulfate. The solvent is removed under reduced pressure and the resulting residue subject

to flash chromatography on silica gel, eluting with mixtures of t-butyl methyl ether and cyclohexane (2:3 to 7:3 v/v), to give a cream solid, which is recrystallized from acetonitrile to give N-(3,5-dichloropyrid-4-yl)-3-cyclopent-3-enyloxy-4-methoxybenzamide (0.54 g), as a white solid, m.p. 193-195°C.

5 [Elemental analysis: C,56.7; H,4.2; N,7.3%; calculated: C,57.0; H,4.3; N,7.4%].

By proceeding in a similar manner, but using 3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzoyl chloride (that is prepared, as described in Reference Example 115, from 3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzoic acid) instead of 3-cyclopent-2-enyloxy-4-methoxybenzoyl chloride in dry tetrahydrofuran, there is prepared N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzamide.

EXAMPLE 29 Compounds GC-GD

A solution of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(methylthio)benzamide (1 g; that is prepared as described in Example 24) in 1 5 dichloromethane (100 mL), containing molecular sieve 4Å, under nitrogen, is treated with 2,6-di-tert-butyl-4-methylpyridine (1.28 g). The resulting mixture is stirred at room temperature for 1.5 hours, and then it is cooled to 0°C (in an ice/salt bath) and treated with xenon difluoride (0.51 g) in one portion. After stirring for a further 2 hours in the cold, the mixture is filtered, and the filtrate is 2 0 washed with saturated aqueous ammonium chloride solution. The organic phase is dried over sodium sulfate and evaporated. The resulting residue is subjected to flash chromatography, eluting with a mixture of ethyl acetate and pentane (2:3 v/v), to give impure N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(fluoromethylthio)benzamide (600 mg). It is further purified by reversed phase 2 5 HPLC on octadecylsilyl silica gel, eluting with a mixture of methanol and water (7:3 v/v), to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(fluoromethylthio)benzamide (519 mg), in the form of a white solid, m.p. 111-113°C. [Elemental analysis: C,51.50; H,4.12; N,6.74%; calculated: C,52.05; H,4.12; N,6.74%].

3 0 By proceeding in a similar manner, but using N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide (that is prepared, as described in Reference Example 24) instead of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(methylthio)benzamide, there is prepared N-(3,5-dichloropyrid-4-yl)-4-(fluoromethylthio)-3-(tetrahydro-3-furyloxy)benzamide.

3 5 EXAMPLE 30 Compounds GE-GF

A suspension of chromium trioxide (0.6 g) in dichloromethane (25 mL) is treated with 3,5-dimethylpyrazole (0.58 g), and stirred for 20 minutes. It is then

treated with a solution of 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)ethanol (1.4 g; that is prepared as described in Reference Example 61) in dichloromethane (10 mL) and the solution is stirred overnight at room temperature. It is then concentrated and the resulting residue is triturated with diethyl ether (200 mL) and filtered. The filtrate is evaporated to give a brown oil, which is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:4 v/v), to give 3-cyclopentyloxy-4-methoxyphenyl 2',6'-dichlorobenzyl ketone (0.36 g), in the form of a white solid, m.p. 135-137°C. [NMR(CDCl₃): 7.73(dd, 1H, J=8Hz, J=2Hz), 7.59(d, 1H, J=Hz), 7.35(d, 2H, J=8Hz), 7.18(t, 1H, J=8Hz), 6.94(d, 1H, J=8Hz), 4.85(m, 1H), 4.66(s, 2H), 3.95(s, 3H), 2.05-1.52(m, 8H). Elemental analysis: C, 62.9, H, 5.3%; calculated: C, 63.3, H, 5.3%].

By proceeding in a similar manner, but using -2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanol (that is prepared as described in Reference Example 61) instead of 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)ethanol, there is prepared 2',6'-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone.

EXAMPLE 31 Compounds GG-GH

A solution of oxalyl chloride (5.3 mL) in dry dichloromethane (125 mL) at -60°C is treated portionwise with dimethyl sulfoxide (9.1 mL) in dichloromethane (20 mL), keeping the temperature below -50°C. The solution is then stirred at -70°C for 20 minutes and is then treated with a suspension of 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol (20.5 g; that is prepared as described in Reference Example 63) in dry dichloromethane (300 mL) during 20 minutes, keeping the temperature below -50°C. After stirring for 30 minutes, the solution is treated with triethylamine (35 mL) and allowed to rise to room temperature. It is then treated with water (250 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are washed with dilute sulfuric acid (100 mL; 1%), aqueous potassium carbonate solution (100 mL; 5%) and brine (100 mL), dried and concentrated and the resulting residue is recrystallized from a mixture of ethyl acetate and heptane, to give 3-cyclopentyloxy-4-methoxyphenyl 3,5-dichloropyrid-4-ylmethyl ketone (19.6 g), m.p. 119-120°C. [NMR(CDCl₃): 8.52(s, 2H), 7.69(dd, 1H, J=8Hz), 7.57(d, 1H, J=2Hz), 6.95(d, 1H, J=8Hz), 4.86(m, 1H), 4.64(s, 2H), 3.95(s, 3H), 2.05-1.58(m, 8H). Elemental analysis: C, 59.8, H, 4.95, N, 3.63%; calculated: C, 60.0, H, 5.0, N, 3.7%].

By proceeding in a similar manner, but using 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanol (that is prepared as described in Reference Example 63) instead of 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol, there is prepared 3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone.

5 Example 32 Compounds GI-GJ

Aqueous 27.5% hydrogen peroxide (0.32 mL) is added to a solution of 3-cyclopentyloxy-4-methoxyphenyl 3,5-dichloropyrid-4-ylmethyl ketone (990 mg) in glacial acetic acid (13 mL). The reaction is heated at 80°C for 8 hours

10 then allowed to stand overnight at room temperature. A further aliquot of aqueous 27.5% hydrogen peroxide (0.32 mL) is added and the mixture heated at 80°C for 2 hours. The reaction mixture is diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate until the washings remained basic. The mixture is washed with brine (50 mL), dried (MgSO₄),

15 concentrated and the residue recrystallized from a mixture of dichloromethane/ethyl acetate/heptane to give 3,5-dichloro-4-(2-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxoethyl)pyridine-N-oxide as a yellow solid, m.p. 179-180°C. [Elemental analysis: C,57.3; H,4.81; N,3.54; Cl,18.0%; calculated for C₁₉H₁₉Cl₂NO₄: C,57.59; H,4.83; N,3.53; Cl,17.89%.]

20 By proceeding in a similar manner, but using 3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone instead of 3-cyclopentyloxy-4-methoxyphenyl 3,5-dichloropyrid-4-ylmethyl ketone, there is prepared 3,5-dichloro-4-(2-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-oxoethyl)pyridine-N-oxide.

25 Example 33 Compounds GK-GL

A solution of diisopropylamine (1.23 mL) in dry tetrahydrofuran (15 mL) is stirred and cooled to -70°C under a nitrogen atmosphere. To this is added a 2.5 M solution of n-butyl lithium in hexanes (3.52 mL) at -70°C. The mixture is stirred for 30 minutes then a solution of 3-chloro-4-methylpyridine (1.02 g) in dry tetrahydrofuran (10 mL) is added. The mixture is stirred for a further 40

30 minutes. A solution of 3-cyclopentyloxy-4,N-dimethoxy-N-methylbenzamide (2.23 g; that is prepared as described Reference Example 64) in dry tetrahydrofuran (10 mL) is added and the mixture stirred at -70°C for 30 minutes, -40°C for 30 minutes, 0°C for 30 minutes, and room temperature for 1

35 hour. A mixture of ethanol and hydrochloric acid 19:1 (40 mL) is added and then the reaction mixture is partitioned between brine (40 mL) and diethyl ether (40 mL). The ethereal phase is dried over sodium sulfate and concentrated in

vacuo to give a pale yellow solid (3.0 g). The solid is triturated with diethyl ether and then purified by flash chromatography (ethyl acetate eluent on a silica gel column) to give a solid (1.6 g). The solid is triturated with diethyl ether, collected and dried to afford 2-(3-chloropyrid-4-yl)-1-(3-cyclopentyloxy-4-methoxyphenyl)ethanone (1.35 g) as a cream solid m.p. 124-125°C. [Elemental analysis: C,66.2; H,5.89; N,4.12%; calculated for C₁₉H₂₀ClNO₃: C,65.99; H,5.83; N,4.05%.]

By proceeding in a similar manner, but using 3-(tetrahydro-3-furyloxy)-4,N-dimethoxy-N-methylbenzamide instead of 3-cyclopentyloxy-4,N-dimethoxy-N-methylbenzamide, there is prepared 2-(3-chloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone.

Example 34 Compounds GM-GN

5% Palladium on carbon (53 mg) is added to a solution of 3-cyclopentyloxy-4-methoxyphenyl 3,5-dichloropyrid-4-ylmethyl ketone (1.9 g) in hot methanol (60 mL) under a nitrogen atmosphere. The mixture is brought to reflux, ammonium formate (1.6 g) is added portionwise during 10 minutes and then refluxing is continued for a further 45 minutes. More 5% palladium on carbon (53 mg) and ammonium formate (1 g) are added and the mixture refluxed for 10 minutes. The reaction mixture is partitioned between dichloromethane (250 mL) and water (100 mL). The organic phase is separated, washed with water (75 mL) and brine (100 mL) and dried over magnesium sulfate. Evaporation yields a yellow gum (1.3 g) which is purified by flash chromatography (ethyl acetate/methanol 19: 1 v/v as eluent on a silica gel column) followed by recrystallization from cyclohexane to give 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethanone (0.55 g) as an off-white solid, m.p. 102-103°C. [Elemental analysis: C,72.6; H,6.63; N,4.23%; calculated for C₁₉H₂₁NO₃: C,73.29; H,6.80; N,4.50%.]

By proceeding in a similar manner, but using 3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone instead of 3-cyclopentyloxy-4-methoxyphenyl 3,5-dichloropyrid-4-ylmethyl ketone, there is prepared 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(4-pyridyl)ethanone.

Example 35 Compounds GO-GP

A solution of 3-cyclopentyloxy-4-methoxybenzonitrile (1.09 g) in dry tetrahydrofuran (3 mL) is added to a 2 M solution of benzylmagnesium chloride in tetrahydrofuran (5.0 mL) at room temperature under a nitrogen atmosphere. The mixture is refluxed for 3 hours, cooled in an ice bath and quenched with

cold 4 M aqueous hydrochloric acid. More tetrahydrofuran (20 mL) is added and the reaction mixture is allowed to stand at room temperature for 48 hours. The tetrahydrofuran layer is decanted and evaporated. The residue is dissolved in cyclohexane (50 mL) and the solution washed successively with water (2 x 10 mL), 5% aqueous sodium bicarbonate (2 x 10 mL), water (2 x 10 mL) and brine (10 mL), and finally dried over magnesium sulfate.

Concentration affords an amber oil (1.53 g) which is purified by flash chromatography (dichloromethane as eluant on silica gel column) to give a pale yellow viscous oil which crystallized on standing. The solid is recrystallized from methanol to afford 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethanone as colorless crystals, m.p. 117-119°C. [Elemental analysis: C, 77.7; H, 7.2%; calculated for C₂₀H₂₂O₃: C, 77.39; H, 7.14%.]

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzonitrile instead of 3-cyclopentyloxy-4-methoxybenzonitrile, there is prepared 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-phenylethanone.

EXAMPLE 36 Compounds GQ-GR

By proceeding in a manner similar to that described in Example 52, but using as the starting material the appropriate quantity of 4-methoxy-3-(3-methyl-2-butenyloxy)benzoic acid and 4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzoic acid, there are prepared:

N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(3-methyl-2-butenyloxy)benzamide, in the form of a white solid, m.p. 173-174°C. [Elemental analysis: C, 56.7; H, 4.9; N, 7.3%; calculated: C, 56.7; H, 7.8; N, 7.35%]; and N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzamide.

EXAMPLE 37 Compounds GS-GT

A solution of 3-[exo-bicyclo-(2.2.1)hept-5-en-2-oxy]-4-methoxybenzoic acid and 4-methoxy-7-oxabicyclo[2.2.1]hept-5-en-2-oxybenzoic acid in dry methylene chloride are treated with oxalyl chloride in a ratio of 4 mm of acid:0.7 mL oxalyl chloride:10 mL of methylene chloride in the presence of a few drops of dimethylformamide under nitrogen and the formed acid chlorides are reacted as in Example 24 to prepare:

N-(3,5-dichloropyrid-4-yl)-3-[exo-bicyclo(2.2.1)-hept-5-en-2-oxy]-4-methoxybenzamide, in the form of white crystals, m.p. 175-176°C. [Elemental analysis: C, 59.3; H, 4.6; N, 6.7%; calculated: C, 59.3; H, 4.5; N, 6.9%]; and N-(3,5-dichloropyrid-4-yl)-4-methoxy-7-oxabicyclo[2.2.1]hept-5-en-2-oxybenzamide.

EXAMPLE 38 Compounds GU-GV

A stirred solution of 3-cyclopentyloxy-4-methoxyaniline (1 g) and triethylamine (0.69 mL) in dry dichloromethane (20 mL) at 0°C is treated dropwise with 2,6-dichlorobenzoyl chloride (1.17 g). After stirring at this temperature for 30 minutes, the mixture is warmed to room temperature and stirred for a further 3 hours. The organic layer is washed with water (100 mL), dried and concentrated. The residue is recrystallized from a mixture of isopropanol and hexane, to give N-(3-cyclopentyloxy-4-methoxyphenyl)-2,6-dichlorobenzamide (0.6 g), m.p. 184-185°C. [Elemental analysis: C,60.2;H,5.0; N,3.6; Cl,18.9%; calculated: C,60.0; H,5.0; N,3.7; Cl,18.65%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)aniline instead of 3-cyclopentyloxy-4-methoxyaniline, there is prepared N-[4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2,6-dichlorobenzamide.

EXAMPLE 39 Compounds GW-GX

By proceeding in a similar manner to that described in Example 38, but using 2,6-difluorobenzoyl chloride instead of 2,6-dichlorobenzoyl chloride, there is prepared N-(3-cyclopentyloxy-4-methoxyphenyl)-2,6-difluorobenzamide, m.p. 150-151°C. [Elemental analysis: C,65.4; H,5.6; N,3.95; F,10.8%; calculated: C,65.7; H,5.5; N,4.0;F,10.9%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)aniline instead of 3-cyclopentyloxy-4-methoxyaniline, there is prepared N-[4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2,6-difluorobenzamide.

EXAMPLE 40 Compounds GY-GZ

A stirred solution of 3-cyclopentyloxy-4-methoxyaniline (1 g) and triethylamine (0.69 mL) in dry dichloromethane (20 mL) is treated dropwise at 0-5°C with a solution of 2,6-dichlorophenyl isocyanate (0.9 g) in dry dichloromethane (10 mL). The resulting mixture is stirred for 30 minutes at this temperature and then for 6 hours at room temperature. The precipitate which forms is collected and stirred with isopropanol (50 mL), with ice cooling. The resulting solid is collected and dried, to give N-(2,6-dichlorophenyl)-N'-(3-cyclopentyloxy-4-methoxyphenyl)urea (1.06 g), m.p. 203-204°C. [Elemental analysis: C,57.2; H,5.0; N,7.0; Cl,18.2%; calculated: C,57.7; H,5.1; N,7.1; Cl,18.0%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)aniline instead of 3-cyclopentyloxy-4-methoxyaniline, there is

prepared N-(2,6-dichlorophenyl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)-phenyl)urea.

EXAMPLE 41 Compounds HA-HB

5 A stirred solution of bis(trichloromethyl) carbonate (0.96 g) in dichloromethane (10 mL) at room temperature is treated with a solution of 3-cyclopentyloxy-4-methoxyaniline (2.0 g) in dichloromethane (10 mL) and then the mixture is stirred for a further 30 minutes during which time a thick precipitate forms. The mixture is diluted with dichloromethane, washed with water (50 mL), dried over magnesium sulfate, and filtered. The solvent is
10 removed in vacuo, to give a light brown oil, which is dissolved in dry tetrahydrofuran (10 mL) to give "solution A".

A stirred solution of 4-amino-3,5-dichloropyridine (1.56 g) in dry tetrahydrofuran (20 mL) under nitrogen at room temperature is treated portionwise with an oil dispersion of sodium hydride (60%; 0.37 g; 10 mmol).
15 After stirring for 15 minutes, the mixture is treated dropwise with "solution A" and then stirred for a further 2 hours, during which time a thick cream precipitate forms. This is filtered off, washed with diethyl ether (20 mL), and then with acetone (20 mL) and dried in vacuo. Recrystallization from methanol gives N-(3,5-dichloropyrid-4-yl)-N'-(3-cyclopentyloxy-4-methoxyphenyl)urea
20 (0.68 g), m.p. 183-184°C. [Elemental analysis: C,54.4; H,4.8; N,10.4; Cl,17.7%; calculated: C,54.6; H,4.8; N,10.6; Cl,17.9%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)aniline instead of 3-cyclopentyloxy-4-methoxyaniline, there is prepared N-(3,5-dichloropyrid-4-yl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)-
25 phenyl)urea.

EXAMPLE 42 Compounds HC-HD

A stirred solution of 3-cyclopentyloxy-4-methoxyphenol (0.2 g) and triethylamine (1.35 mL) in dichloromethane (5 mL) is treated portionwise at 0-5°C with 2,6-dichlorobenzoyl chloride (0.28 g), and the solution is warmed to
30 room temperature and stirred for a further 2 hours. The reaction mixture is poured into hydrochloric acid (50 mL; 2 N) and is extracted with diethyl ether (3 x 50 mL). The combined organic extracts are then washed with water (100 mL), and brine (100 mL), dried over magnesium sulfate and concentrated. The residual oil is subjected to flash chromatography on silica gel, eluting with a
35 mixture of pentane and ethyl acetate (4:1 v/v), to give 3-cyclopentyloxy-4-methoxyphenyl 2,6-dichlorobenzoate (0.28 g), m.p. 100-101°C. [Elemental analysis: C,59.7; H,4.7%; calculated: C,59.9; H,4.8%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)phenol instead of 3-cyclopentyloxy-4-methoxyphenol, there is prepared 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl 2,6-dichlorobenzoate.

EXAMPLE 43 Compounds HE-HF

5 A stirred solution of 3-cyclopentyloxy-4-methoxyphenol (0.5 g), potassium carbonate (0.4 g) and alpha 2,6-trichlorotoluene (0.56 g) in dimethylformamide (5 mL) is heated at 100°C for 1 hour. The solution is then concentrated and the residue is subjected to flash chromatography, eluting with a mixture of dichloromethane and pentane (1:1 v/v), to give

10 3-cyclopentyloxy-4-methoxyphenyl 2,6-dichlorobenzyl ether (0.76 g), m.p. 96-98°C. [Elemental analysis: C,61.7; H,5.5%; calculated: C,62.1; H,5.5%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)phenol instead of 3-cyclopentyloxy-4-methoxyphenol, there is prepared 2,6-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ether.

15 EXAMPLE 44 Compounds HG-HH

A solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (5 g) and 2-chloroaniline (2.5 mL) in toluene (60 mL) is heated at reflux under a Dean and Stark water trap for 3 hours. After concentration, the residue is dissolved in methanol (60 mL) and the stirred solution is treated at 0°C with sodium
20 cyanoborohydride (2.1 g). The temperature is allowed to rise to room temperature, and the stirring is continued for 2 hours, before dilution with ethyl acetate (100 mL) and washing with saline (100 mL). The organic layer is dried and concentrated, to give a brown oil. This oil is subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate and
25 hexane (1:4v/v), to give N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzylamine (0.64 g), in the form of an oil. [Elemental analysis: C,69.5; H,6.8; N,4.1; Cl,10.6%; calculated: C,68.8; H,6.7; N,3.2; Cl,10.7%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde instead of 3-cyclopentyloxy-4-methoxybenzaldehyde,
30 there is prepared N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzylamine.

EXAMPLE 45 Compounds HI-HJ

A stirred suspension of 2,6-dichlorobenzyltriphenylphosphonium bromide (2.5 g) in dry tetrahydrofuran (30 mL) is treated dropwise with a
35 solution of potassium t-butoxide (0.56 g) in dry tetrahydrofuran (32 mL) at 0°C. After stirring at this temperature for 1 hour, it is treated with a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (1.1 g) in dry tetrahydrofuran (15 mL).

The reaction mixture is stirred from 0°C to 5°C for 1 hour and 30 minutes, and then allowed to warm to room temperature. After stirring overnight, the mixture is concentrated and the resulting residue is treated with ethyl acetate (200 mL). The resulting organic solution is filtered. The filtrate is concentrated and the

5. resulting residue is subjected to flash chromatography, eluting with dichloromethane, to give trans-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)ethene (1.16 g), m.p. 47-49°C. [Elemental analysis: C,66.4; H,5.6; Cl,19.4%, calculated: C,66.1; H,5.55; Cl,19.5%].

- 10 By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde instead of 3-cyclopentyloxy-4-methoxybenzaldehyde, there is prepared trans-2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene.

EXAMPLE 46 Compounds HK-HL

- 15 By proceeding in a manner similar to that described in Example 45, but using 2,6-difluorobenzyltriphenylphosphonium bromide, there is prepared trans-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl)ethene, m.p. 65-67°C. [Elemental analysis: C,73.0; H,6.1%; calculated: C,72.7; H,6.1%].

- 20 By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde instead of 3-cyclopentyloxy-4-methoxybenzaldehyde, there is prepared trans-2-(2,6-difluorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene.

EXAMPLE 47 Compounds HM-HN

- 25 Pyridinium dichromate (3.6 g) in dry dichloromethane (40 mL) under nitrogen is treated with (±)-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(pyrid-4-yl)ethanol (2.0 g; that is prepared as described in Reference Example 67), in one portion. The resulting mixture is stirred for 1 hour and 30 minutes, and then filtered through a pad of diatomaceous earth, and the pad is washed with diethyl ether. The combined filtrate and ethereal washings are washed with saturated aqueous cupric sulfate solution (2 x 30 mL), followed by water
30 (30 mL), and then dried over magnesium sulfate. The solvent is removed under reduced pressure, and the resulting oily residue is subjected to flash chromatography on silica gel, eluting with ethyl acetate, to give 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(pyrid-4-yl)ethane-1,2-dione (0.4 g), in the form of a yellow solid, m.p. 117-119°C. [Elemental analysis: C,70.1; H,6.0; N,4.1%; calculated: C,70.1; H,5.9; N,4.3%].
35

By proceeding in a similar manner, but using (±)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(pyrid-4-yl)ethanol instead of (±)-1-(3-

cyclopentyloxy-4-methoxyphenyl)-2-(pyrid-4-yl)ethanol, there is prepared 1-[(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2-(pyrid-4-yl)ethane-1,2-dione.

EXAMPLE 48 Compounds HO-HP

A stirred solution of diisopropylamine (3.6 mL) in dry tetrahydrofuran (132 mL) is treated with a solution of butyl lithium in hexanes (10.3 mL; 2.5 M), dropwise, under nitrogen, keeping the temperature below -65°C. The resulting mixture is then stirred for a further period of 20 minutes, at below -65°C. The stirred mixture, still maintained at below -65°C, is then treated dropwise with a solution of 3,5-dichloropyridine (3.5 g) in dry tetrahydrofuran (24 mL). The stirred mixture is maintained at below -65°C for a further 30 minutes. The stirred mixture, still maintained at below -65°C, is then treated portionwise with 3-cyclopentyloxy-4-methoxyphenyldiazonium tetrafluoroborate (7.2 g), and it is stirred at below -65°C for a further 45 minutes. The resulting mixture is then allowed to warm to room temperature overnight. It is then treated with water (600 mL), the layers are separated, and the aqueous layer is further extracted with diethyl ether (3 x 100 mL). The combined organic extracts are washed with saturated aqueous sodium chloride solution (100 mL), dried over magnesium sulfate, and then evaporated to dryness. The resulting residue is subjected to flash chromatography on silica gel, eluting with a mixture of pentane and diethyl ether (2:1 v/v), to give a red solid (3.1 g) which, on recrystallization from pentane, gives trans-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloropyrid-4-yl)diazene (2.2 g), in the form of a red-brown solid, m.p. 88-89°C. [Elemental analysis: C, 56.0; H, 4.8; N, 11.3%; calculated: C, 55.75; H, 4.7; N, 11.5%].

By proceeding in a similar manner, but using 4-methoxy-3-(tetrahydro-3-furyloxy)phenyldiazonium tetrafluoroborate instead of 3-cyclopentyloxy-4-methoxyphenyldiazonium tetrafluoroborate, there is prepared trans-2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)diazene.

EXAMPLE 49 Compounds HQ-HT

A solution of trans-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloropyrid-4-yl)diazene (1.2 g; that is prepared as described in Example 48) in dichloromethane (24 mL) is treated portionwise with metachloroperbenzoic acid (0.6 g). The resulting mixture is stirred in the dark for 2 hours and 30 minutes, and then it is allowed to stand in the dark overnight. After the addition of a further quantity of dichloromethane (24 mL), the mixture is shaken with saturated aqueous sodium bicarbonate solution (12 mL). The layers are separated and the aqueous phase is further extracted with dichloromethane

(3 x 6 mL). The combined organic extracts are washed with saturated aqueous sodium carbonate solution (6 mL), dried over magnesium sulfate, and evaporated to dryness. The resulting residual gum is dissolved in a mixture of dichloromethane and diisopropyl ether (1:2 v/v), and treated with activated carbon. After filtration, the solution is concentrated to low bulk. The resulting crystalline solid is filtered off and washed with diisopropyl ether and pentane, and dried in air. This material (0.71 g) is subjected to flash chromatography on silica gel, eluting initially with dichloromethane, and then with a mixture of dichloromethane and methanol (19:1v/v), to give a solid (0.58 g), which is purified by reverse phase high pressure liquid chromatography on octadecylsilyl silica gel, eluting with a mixture of methanol and water (3:1 v/v) to yield:

1-(3-cyclopentyloxy-4-methoxyphenyl)-c-1-oxo-r-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene (0.17 g) is eluted first, in the form of a yellow solid, m.p. 139-141°C. [Elemental analysis: C,51.4; H,4.4; N,10.4%; calculated: C,51.3; H,4.3; N,10.6%]; and

trans-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene (0.31 g) is eluted second, in the form of a red solid, m.p. 172-174°C [Elemental analysis: C,53.4; H,4.5; N,10.9%; calculated: C,53.4; H,4.5; N,11.0%].

By proceeding in a similar manner, but using trans-2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)diazene instead of trans-2-(3,5-dichloropyrid-4-yl)-1-(3-cyclopentyloxy-4-methoxyphenyl)diazene, there are prepared:

1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-c-1-oxo-r-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene; and

trans-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene.

EXAMPLE 50 Compounds HU-HV

A stirred solution of N-(3-hydroxy-4-methoxyphenylsulfonyl)-2-chloroaniline, containing some N,N-bis(3-hydroxy-4-methoxyphenyl-sulfonyl)-2-chloroaniline (0.7 g; that is prepared as described in Reference Example 72) in dimethylformamide (20 mL) is treated portionwise with an oil dispersion of sodium hydride (60%; 0.11 g, 2.7 mmol) and the mixture is stirred at 60°C for 1 hour. It is then treated dropwise with cyclopentyl bromide (0.32 mL) and the solution is stirred at 60°C for a further period of 4 hours. After cooling, the mixture is treated with water (20 mL) and extracted with diethyl ether (2 x 75

mL). The organic extracts are combined, dried and evaporated, to give an oil which is subjected to flash chromatography on silica gel, eluting with diethyl ether, to give N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzenesulfonamide (150 mg), m.p. 113-115°C. [NMR(CDCl₃): 7.68(dd, 1H, J=8Hz, J=2Hz), 7.37(dd, 1H, J=8Hz, J=2Hz), 7.26(d, 1H, J=2Hz), 7.24(dt, 1H, J=8Hz, J=2Hz), 7.13(d, 1H, J=2Hz), 7.04(dt, 1H, J=8Hz, J=2Hz), 6.92(bs, 1H), 6.82(d, 1H, J=8Hz), 4.65(m, 1H), 3.86(s, 3H), 1.92-1.55 (m, 8H)].

By proceeding in a similar manner, but using tetrahydrofuryl bromide instead of cyclopentyl bromide, there is prepared N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzenesulfonamide.

EXAMPLE 51 Compounds HW-HX

Sodium hydride (0.14 g) is added to a solution of 3,5-dichloro-4-aminopyridine (0.28 g) in dimethylformamide (7 mL) under nitrogen and the mixture is stirred at room temperature for 15 minutes. A solution of 3-cyclopentyloxy-4-trifluoromethoxybenzoyl chloride (0.54 g) in dimethylformamide (3 mL) is then added dropwise and the mixture is stirred at room temperature for 3 hours. Water (50 mL) is added and the mixture is extracted with ethyl acetate (2 x 75 mL). The combined extracts are dried over magnesium sulfate and evaporated under reduced pressure, to give a brown oil, which is subjected to mplc, eluting with a mixture of diethyl ether and pentane (3:7 v/v), to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-trifluoromethoxybenzamide (0.6 g), in the form of a white solid. m.p. 129-131°C, Elemental analysis: C, 50.0; H, 3.5; N, 6.6; Cl, 16.3%; calculated: C, 49.7; H, 3.5; N, 6.4; Cl, 16.2%.

By proceeding in a similar manner, but using 3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzoyl chloride instead of 3-cyclopentyloxy-4-trifluoromethoxybenzoyl chloride, there is prepared N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzamide.

EXAMPLE 52 Compounds HY-HZ

A stirred solution of 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoic acid (0.7 g) in acetone (24 mL) is treated with triethylamine (0.4 mL) and cyanuric chloride (0.24 g) and the solution is stirred for 4 hours at room temperature. The precipitated solid is filtered off and the filtrate is evaporated to dryness in vacuo. The residue is treated with dry tetrahydrofuran (12 mL) and filtered, to give "solution A", containing 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoyl chloride.

A stirred solution of 3,5-dichloro-4-aminopyridine (0.42 g) in dry tetrahydrofuran (24 mL) at room temperature is treated with sodium hydride (60% dispersion in oil; 0.21 g), portionwise, under nitrogen and stirred for 2 hours. It is then treated, dropwise, with "solution A" and stirred at room temperature for 3 hours. The reaction mixture is diluted with water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The extract is washed with water, dried over magnesium sulfate and concentrated. The residue is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:1 v/v), to give N-(3,5-dichloropyrid-4-yl)-3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzamide (0.44 g), m.p. 102-104°C. [Elemental analysis: C, 52.4; H, 3.15; Cl, 16.8; N, 6.7%; calculated: C, 52.3; H, 2.9; Cl, 16.8; N, 6.7%].

By proceeding in a similar manner, but using 3-(4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzoic acid instead of 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoic acid, there is prepared N-(3,5-dichloropyrid-4-yl)-3-(4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide.

EXAMPLE 53 Compounds IA-IB

By proceeding as described in Example 3, but using the appropriate quantities of 3-isopropoxy-4-difluoromethoxybenzoic acid and 4-amino-3,5-difluoropyridine, there is prepared N-(3,5-difluoropyrid-4-yl)-3-isopropoxy-4-difluoromethoxybenzamide, in the form of a white solid, m.p. 101-103°C, [Elemental analysis: C, 53.7; H, 4.0; N, 7.7%; calculated: C, 53.6; H, 3.9; N, 7.8%].

By proceeding in a similar manner, but using 4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzoic acid instead of 3-isopropoxy-4-difluoromethoxybenzoic acid, there is prepared N-(3,5-difluoropyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide.

EXAMPLE 54 Compounds IC-ID

By proceeding as described in Example 13, but using the appropriate quantity of N-(3,5-difluoropyrid-4-yl)-3-isopropoxy-4-difluoromethoxybenzamide, there is prepared N-(3,5-difluoro-1-oxido-4-pyridinio)-3-isopropoxy-4-difluoromethoxybenzamide in the form of a white solid, m.p. 55°C, [Elemental analysis: C, 50.2; H, 3.7; N, 7.5%; calculated (for a form containing 0.5 molecules of water per molecule): C, 50.1; H, 4.0; N, 7.3%].

By proceeding in a similar manner, but using N-(3,5-difluoropyrid-4-yl)-3-(1-methoxy-prop-2-oxy)-4-difluoromethoxybenzamide instead of N-(3,5-difluoropyrid-4-yl)-3-isopropoxy-4-difluoromethoxybenzamide, there is

prepared N-(3,5-difluoro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide.

EXAMPLE 55 Compounds IE-IF

By proceeding as described in Reference Example 7 and Example 3, but using the appropriate quantities of 3-isopropoxy-4-difluoromethoxybenzoic acid and 4-amino-3,5-dichloropyridine, there is prepared N-(3,5-dichloro-pyrid-4-yl)-3-isopropoxy-4-difluoromethoxybenzamide, in the form of a white solid, m.p. 113-114°C, [Elemental analysis: C,49.3; H,3.7; N,7.1%; calculated: C,49.1; H,3.6; N,7.1%].

By proceeding in a similar manner, but using 4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzoic acid instead of 3-isopropoxy-4-difluoromethoxybenzoic acid, there is prepared N-(3,5-dichloro-pyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide.

EXAMPLE 56 Compounds IG-IH

By proceeding as described in Example 13, but using the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-isopropoxybenzamide, there is prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-3-isopropoxy-4-difluoromethoxybenzamide, in the form of a white solid, m.p. 138-140°C, [Elemental analysis: C,46.1; H,3.7; Cl,17.0; N,6.8%; calculated (for a form containing 0.5 molecules of water per molecule): C,46.2; H,3.6; Cl,17.0; N,6.7%].

By proceeding in a similar manner, but using N-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide instead of N-(3,5-dichloropyrid-4-yl)-4-difluoromethoxy-3-isopropoxybenzamide, there is prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide.

EXAMPLE 57 Compounds II-IJ

By proceeding as described in Example 3, but using the appropriate quantity of 3-(exo)-8,9,10-trinorborn-2-yloxy-4-difluoromethoxybenzoic acid, there is prepared N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxybenzamide in the form of a white solid, m.p. 152-154°C, [Elemental analysis: C,54.4; H,4.1; N,6.3%; calculated: C,54.2; H,4.1; N,6.3%].

By proceeding in a similar manner, but using 3-(7-oxa-bicyclo[2.2.1]-heptan-2-oxy)-4-difluoromethoxybenzoic acid instead of 3-(exo)-8,9,10-trinorborn-2-yloxy-4-difluoromethoxybenzoic acid, there is prepared N-(3,5-

dichloro-4-pyridyl)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide.

EXAMPLE 58 Compounds IK-IL

By proceeding as described in Example 13, but using the appropriate quantity of N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxybenzamide and N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide, there are prepared:

- N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxybenzamide, m.p. 101-103°C; and
- 1 0 N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide.

EXAMPLE 59 Compounds IM-IN

A suspension of 3-(2-fluorocyclopentyloxy)-4-methoxybenzoic acid (0.48 g) in toluene (20 mL) is treated with thionyl chloride (0.34 g) and then is heated

1 5 at 60°C for 3 hours, and cooled and evaporated to give 3-(2-fluorocyclopentyloxy)-4-methoxybenzoyl chloride.

A suspension of sodium hydride (0.3; 60% oil dispersion) in dimethylformamide (5 mL) is treated with 4-amino-3,5-dichloropyridine (0.62 g) and the mixture is stirred for 40 minutes. A solution of 3-(2-fluoro-

2 0 cyclopentyloxy)-4-methoxybenzoyl chloride in dimethylformamide (12 mL) is added, and the mixture is stirred at 80-90°C for 1 day. The solution is cooled, poured into water (75 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts are washed with brine (50 mL), dried over magnesium sulfate and concentrated. The residue is subjected to flash

2 5 chromatography, eluting with a mixture of ethyl acetate and petroleum ether (1:3 v/v), to give N-(3,5-dichloropyrid-4-yl)-3-(2-fluorocyclopentyloxy)-4-methoxybenzamide (0.26 g), m.p. 167-169°C. [Elemental analysis: C, 53.8; H, 4.2; N, 6.75; Cl, 17.8%; calculated: C, 54.15; H, 4.3; N, 7.0; Cl, 17.8%].

By proceeding in a similar manner, but using 4-methoxy-3-[2-(prop-2-yn-1-oxy)ethoxy]benzoic acid instead of 3-(2-fluorocyclopentyloxy)-4-methoxybenzoic acid, there is prepared N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[2-(prop-2-yn-1-oxy)ethoxy]benzamide.

3 0

EXAMPLE 60 Compounds IO-IP

By proceeding in a similar manner as in Example 59, but using the appropriate quantity of 3-(tetrahydrothiophen-3-oxy)-4-methoxybenzoic acid and 3-(4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzoic acid, there are prepared:

3 5

N-(3,5-dichloropyrid-4-yl)-3-(tetrahydrothiophen-3-oxy)-4-methoxybenzamide, in the form of a white solid, m.p. 160-162°C, [Elemental analysis: C,51.1; H,4.0; Cl,17.6; N,7.2%; calculated: C,51.1; H,4.0; Cl,17.8; N,7.0%]; and
5 N-(3,5-dichloro-1-oxido-4-pyridinio)-3-(4,4-dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide.

EXAMPLE 61 Compounds IQ-IR

By proceeding in a manner similar to that described in Example 24, but using as the starting material the appropriate quantity of 3-isopropoxy-4-(methylthio)benzoyl chloride and 3-isopropoxy-4-(methylthio)benzoyl chloride,
10 there are prepared:

N-(3,5-dichloropyrid-4-yl)-3-isopropoxy-4-(methylthio)benzamide, in the form of a white solid, m.p. 146-148°C. [Elemental analysis: C,51.9; H,4.5; N,7.4; Cl,18.8; S,8.5%; calculated: C,51.7; H,4.3; N,7.5; Cl,19.1%]; and
N-(3,5-dichloropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)benzamide.

15 EXAMPLE 62 Compounds IS-IT

By proceeding in a manner similar to that described in Example 24, but using as the starting material the appropriate quantities of 3-isopropoxy-4-(methylthio)benzoyl chloride and 4-amino-3,5-difluoropyridine, there is prepared N-(3,5-difluoropyrid-4-yl)-3-isopropoxy-4-(methylthio)benzamide, in
20 the form of a white solid, m.p. 175-177°C. [Elemental analysis: C,56.6; H,4.8; N,8.2; S,9.7%; calculated: C,56.8; H,4.8; N,8.3; S,9.5%].

By proceeding in a similar manner, but using 3-(1-methoxyprop-2-oxy)-4-(methylthio)benzoyl chloride instead of 3-isopropoxy-4-(methylthio)benzoyl chloride, there is prepared N-(3,5-difluoropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-
25 4-(methylthio)benzamide.

EXAMPLE 63 Compounds IU-IV

By proceeding in a manner similar to that described in Example 24, but using as the starting material the appropriate quantity of 3-(pent-3-yloxy)-4-(methylthio)benzoyl chloride and 3-(3-methoxybutoxy)-4-(methylthio)benzoyl
30 chloride, there are prepared:

N-(3,5-dichloropyrid-4-yl)-3-(pent-3-yloxy)-4-(methylthio)benzamide, in the form of a white solid, m.p. 154-155°C. [Elemental analysis: C,53.8; H,4.9; N,7.0; S,7.8%; calculated: C,54.14; H,5.05; N,7.0; S,8.0%]; and
N-(3,5-dichloropyrid-4-yl)-3-(3-methoxybutoxy)-4-(methylthio)benzamide.

35 EXAMPLE 64 Compounds IW-IX

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of rac-1-[3-((exo)-8,9,10-

trinorbornyl-2-oxy}-4-methoxyphenyl]-2-(3,5-dichloropyrid-4-yl)ethanol there is prepared, after flash chromatography, eluting with a mixture of ethyl acetate and pentane (1:2 v/v), (\pm)-1-[3-((exo)-8,9,10-trinorbornyl-2-oxy)-4-methoxyphenyl]-2-(3,5-dichloropyrid-4-yl)ethanone, in the form of a white solid, m.p. 113-114°C. [Elemental analysis: C,61.9; H,5.2; N,3.4%; calculated: C,62.1; H,5.2; N,3.4%].

By proceeding in a similar manner, but using 1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]-2-(3,5-dichloropyrid-4-yl)ethanol instead of rac-1-[3-((exo)-8,9,10-trinorbornyl-2-oxy)-4-methoxyphenyl]-2-(3,5-dichloropyrid-4-yl)ethanol, there is prepared 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone.

EXAMPLE 65 Compounds IY-IZ

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 1-(3-cyclopentyloxy-4-(methylthio)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanol and 1-(3-(tetrahydro-3-furyloxy)-4-(methylthio)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanol, there are prepared:

1-[3-cyclopentyloxy-4-(methylthio)phenyl]-2-(3,5-dichloropyrid-4-yl)ethanone in the form of a yellow solid, m.p. 110-111°C. [Elemental analysis: C,57.6; H,4.8; Cl,17.8; N,3.4%; calculated: C,57.6; H,4.8; Cl,17.9; N,3.5%]; and 1-[3-(tetrahydro-3-furyloxy)-4-(methylthio)phenyl]-2-(3,5-dichloropyrid-4-yl)ethanone.

EXAMPLE 66 Compounds JA-JB

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol and 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanol, there are prepared:

1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone, in the form of a buff solid, m.p. 153-155°C. [Elemental analysis: C,56.9; H,4.83; N,3.85%; calculated: C,57.64; H,4.84; N,3.95%]; and 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone.

EXAMPLE 67 Compounds JC-JD

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 1-(4-methylthio-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol and 2-(3,5-dichloropyrid-

4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanol, there are prepared:

1-(4-methylthio-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone, in the form of a white solid, m.p. 116-117°C. [Elemental analysis: C,55.0; H,4.59;

5. Cl,19.1; N,3.68; S,8.6%; calculated: C,55.14; H,4.63; Cl,19.2; N,3.78; S,8.7%]; and

2-(3,5-dichloropyrid-4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone.

EXAMPLE 68 Compounds JE-JF

1 0 Hydrogen peroxide (8 mL) is added to a stirred suspension of 1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone (5.97 g) in glacial acetic acid (17 mL). The mixture is stirred at 70-80°C for 3 hours. After cooling, the mixture is basified by treatment with aqueous sodium hydroxide (6 M), and extracted with ethyl acetate. The extracts are washed with brine, dried
1 5 over magnesium sulfate and evaporated, to give a white solid which is triturated with pentane and dried at 80°C, to give 1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloro-1-oxido-4-pyridinio)ethanone, in the form of a white solid, m.p. 167-169°C. [Elemental analysis: C,55.4; H,4.61; Cl,19.3; N,3.72%, calculated: C,55.15; H,4.63; Cl,19.2; N,3.78%].

2 0 By proceeding in a similar manner, but using 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone instead of 1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone, there is prepared 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone.

2 5 EXAMPLE 69 Compounds JG-JH

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 1-(3-cyclopentyloxy-4-difluoromethoxyphenyl)-2-(3,5-dichloropyrid-4-yl)-ethanol and 2-(3,5-dichloropyrid-4-yl)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-ethanol, there are prepared:

3 0 1-(3-cyclopentyloxy-4-difluoromethoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone, in the form of a white solid, m.p. 80-82°C. [Elemental analysis: C,55.1; H,4.1; N,3.2%; calculated: C,54.8; H,4.1; N,3.4%]; and
3 5 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanone.

EXAMPLE 70 Compounds JI-JJ

By proceeding in a manner similar to that described in Example 13, but using as the starting material the appropriate quantity of 1-(3-cyclopentyloxy-4-difluoromethoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanone and 2-(3,5-dichloropyrid-4-yl)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)-phenyl)ethanone, there are prepared:

1-(3-cyclopentyloxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxido-4-pyridinio)ethanone, in the form of a white solid, m.p. 178-179°C. [Elemental analysis: C,53.1; H,4.1; N,3.1%; calculated: C,52.8; H,4.0; N,3.2%]; and 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone.

EXAMPLE 71 Compounds JK-JL

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 2-(3,5-dichloro-pyrid-4-yl)-1-[3-((exo)-bicyclo(2.2.1)hept-5-en-2-yloxy)-4-methoxyphenyl]ethanol and 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanol, there are prepared:

2-(3,5-dichloropyrid-4-yl)-1-[3-((exo)-bicyclo(2.2.1)hept-5-en-2-yloxy)-4-methoxyphenyl]ethanone, in the form of a white solid, m.p. 89-91°C. [Elemental analysis: C,62.6; H,4.75; N,3.4%; calculated: C,62.4; H,4.7; N,3.5%]; and

2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanone.

EXAMPLE 72 Compounds JM-JN

By proceeding in a manner similar to that described in Example 31, but using as the starting material the appropriate quantity of 2-(3,5-dichloro-4-pyridyl)-1-[4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxyphenyl]ethanol and 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl)ethanol, there are prepared:

2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxyphenyl)ethanone, in the form of a white solid, m.p. 120-122°C; and 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl)ethanone.

EXAMPLE 73 Compounds JO-JP

By proceeding in a manner similar to that described in Example 13, but using as the starting material the appropriate quantity of 2-(3,5-dichloro-4-pyridyl)-1-[4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxyphenyl]-

ethanone and 2-(3,5-dichloro-4-pyridyl)-1-[4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone, there are prepared: 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-[4-difluoromethoxy-3-(exo)-8,9,10-trinorborn-2-yloxyphenyl]ethanone, in the form of a white solid, m.p. 59-61°C;

5. and

2-(3,5-dichloro-1-oxido-4-pyridinio)-1-[4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone.

EXAMPLE 74 Compounds JQ-JR

By proceeding in a manner similar to that described in Example 31, but
1 0 using as the starting material the appropriate quantity of 2-(3,5-dichloro-4-pyridyl)-1-[4-methoxy-3-(3-methyl-2-butenyloxy)-phenyl]ethanol and 2-(3,5-dichloro-4-pyridyl)-1-[3-(2-isopropoxyethoxy)-4-methoxyphenyl]ethanol, there are prepared:

2-(3,5-dichloro-4-pyridyl)-1-[4-methoxy-3-(3-methyl-2-butenyloxy)-
1 5 phenyl]ethanone, in the form of a white solid, m.p. 115-117°C; and 2-(3,5-dichloro-4-pyridyl)-1-[3-(2-isopropoxyethoxy)-4-methoxyphenyl]-ethanone.

EXAMPLE 75 Compounds JS-JT

By proceeding in a manner similar to that described in Example 30, but
2 0 using as the starting material the appropriate quantity of 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-isopropoxyphenyl)ethanol and 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanol, there are prepared:

2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-isopropoxyphenyl)ethanone
2 5 in the form of a white solid, m.p. 85-87°C. [Elemental analysis: C,52.7; H,3.85; N,3.6%; calculated: C,52.3; H,3.9; N,3.6%]; and 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)-phenyl)ethanone.

EXAMPLE 76 Compounds JU-JV

By proceeding in a manner similar to that described in Example 13, but
3 0 using as the starting material the appropriate quantity of 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-isopropoxyphenyl)ethanone and 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone, there are prepared

3 5 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-isopropoxyphenyl)ethanone, in the form of a white solid, m.p. 138-140°C.

[Elemental analysis: C,50.3; H,3.7; N,3.2; Cl,17.6%; calculated: C,50.2; H,3.7; N,3.45; Cl,17.45%]; and
2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone.

5 EXAMPLE 77 Compounds JW-JX

By proceeding in a manner similar to that described in Example 43, but using as the starting material the appropriate quantity of 4-bromomethyl-3,5-dichloropyridine, there is prepared 3,5-dichloro-4-(3-cyclopentyloxy-4-methoxyphenoxy-methyl)pyridine, in the form of a white solid, m.p. 75-77°C.

10 By proceeding in a similar manner, but using 4-bromomethyl-3,5-dichloropyridine and 4-methoxy-3-(tetrahydro-3-furyloxy)phenol, there is prepared 3,5-dichloro-4-(4-methoxy-3-(tetrahydro-3-furyloxy)phenoxy-methyl)pyridine.

EXAMPLE 78 Compounds JY-JZ

15 By proceeding in a manner similar to that described in Example 13, but using as the starting material the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorborn-2-yloxybenzamide and N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide, there are prepared:
20 N-(3,5-dichloro-1-oxido-4-pyridinio-4-methoxy-3-(exo)-8,9,10-trinorborn-2-yloxy-benzamide, m.p. 130-132°C; and
N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide.

EXAMPLE 79 Compounds KA-KB

25 A suspension of 3-cyclopentyloxy-6-fluoro-4-methoxybenzoic acid (0.88 g, that is prepared as described in Reference Example 113) in dry toluene (10 mL) is treated with thionyl chloride (2 mL) and the mixture is refluxed for 90 minutes. The mixture is cooled and concentrated in vacuo, to give "yellow oil A".

30 A suspension of sodium hydride (0.4 g of a 60% dispersion in mineral oil) in dimethylformamide (5ml) is treated with a solution of 4-amino-3,5-dichloropyridine (0.82 g) in dimethylformamide (5 mL) and the reaction mixture is stirred at room temperature for 30 minutes. It is then treated with a solution of the "yellow oil A" in dimethylformamide (5 mL) and stirred at 45°C for 16 hours. It is then cooled, poured into water (50 mL) and extracted with chloroform
35 (3x500 mL). The combined extracts are dried over magnesium sulphate and concentrated. The residual yellow oil is subjected to flash chromatography [a 3:1 mixture of petroleum ether (b.p.60-80°C) and ethyl acetate is used as

eluent in a silica gel column] to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-6-fluoro-4-methoxybenzamide (0.77 g), in the form of a white solid, m.p. 143-144°C. [Elemental analysis: C,53.75; H,4.28; N,7.29%; calculated:- C,54.15; H,4.29; N,7.02%. NMR (CDCl₃): 8.56(s,1H), 8.37(d,1H,J=18Hz), 7.62(d,1H,J=8Hz), 6.71(d,1H,J=14Hz), 4.87-4.82(m,1H), 3.93(s,3H), 2.03-1.57(m,8H)].

By proceeding in a similar manner, but using 6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid instead of 3-cyclopentyloxy-6-fluoro-4-methoxybenzoic acid, there is prepared N-(3,5-dichloropyrid-4-yl)-6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

EXAMPLE 80 Compounds KC-KD

Thionyl chloride (0.78 mL) is added to a solution of 5-cyclopentyloxy-6-methoxynicotinic acid (850 mg; that is prepared as in Reference Example 48) and dimethylformamide (1 drop) in toluene (60 mL). The mixture is heated and stirred at reflux for 1 hour. The mixture is cooled and concentrated to give crude 5-cyclopentyloxy-6-methoxynicotinoyl chloride.

Sodium hydride (320 mg of a 60% dispersion in oil) is added to a stirred solution of 4-amino-3,5-dichloropyridine (649 mg) in dry dimethylformamide (20 mL) under nitrogen. The mixture is stirred at room temperature for 30 minutes, and then it is treated, dropwise, with a solution of the 5-cyclopentyloxy-6-methoxynicotinoyl chloride in dry dimethylformamide (10 mL). After 3 hours, the mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate extract is washed with water, dried over magnesium sulphate, and concentrated in vacuo to give a buff solid which is triturated with methyl tert-butyl ether, to give 5-cyclopentyloxy-N-(3,5-dichloropyrid-4-yl)-6-methoxynicotinamide (500 mg) in the form of a white solid, m.p. 182-183°C. [Elemental analysis: C,53.4; H,4.45; Cl,18.6; N,10.9%; calculated: C,53.4; H,4.48; Cl,18.55; N,10.99%.]

By proceeding in a similar manner, but using 6-methoxy-5-(tetrahydro-3-furyloxy)nicotinic acid instead of 5-cyclopentyloxy-6-methoxynicotinic acid, there is prepared N-(3,5-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide.

EXAMPLE 81 Compounds KE-KJ

Thionyl chloride (0.46 mL) is added to a solution of 5-cyclopentyloxy-6-methoxynicotinic acid (500 mg; that is prepared as in Reference Example 48) and dimethylformamide (1 drop) in toluene (10 mL). The mixture is heated and stirred at reflux for 1 hour. The mixture is cooled and concentrated to give

crude 5-cyclopentyloxy-6-methoxynicotinoyl chloride, in the form of a yellow oil which slowly crystallized.

Sodium hydride (128 mg of a 60% dispersion in oil) is added to a stirred solution of 2,6-dichloroaniline (263 mg) in dry tetrahydrofuran (10 mL) under a nitrogen atmosphere. The mixture is stirred at room temperature for 45 minutes, and then it is treated, dropwise, with a solution of 5-cyclopentyloxy-6-methoxynicotinoyl chloride in dry tetrahydrofuran (5 mL). After 3 hours the mixture is concentrated, treated with water, and extracted with ethyl acetate. The extract is dried over magnesium sulphate and concentrated, to give a brown oil. Trituration of the oil with methyl tert-butyl ether gave 250 mg of N-(2,6-dichlorophenyl)-5-cyclopentyloxy-6-methoxynicotinamide, in the form of a white solid, m.p. 145-146°C. [Elemental analysis: C,56.7; H,4.79; Cl,18.5; N,7.4%; calculated: C,56.7; H,4.76; Cl,18.6; N,7.35%].

By proceeding in a similar manner, but using 6-methoxy-5-(tetrahydro-3-furyloxy)nicotinic acid instead of 5-cyclopentyloxy-6-methoxynicotinic acid, there is prepared N-(2,6-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide.

By proceeding in a similar manner, but using the appropriate quantities of the appropriate carboxylic acids (that are prepared as in Reference Examples 48, 50 and 115) and amines, there are prepared:-

(after trituration with n-pentane and methyl tert-butyl ether)
5-cyclopentyloxy-N-(3,5-difluoropyrid-4-yl)-6-methoxynicotinamide, in the form of a white solid, m.p. 210-211°C. [Elemental analysis: C,58.4; H,4.93; N,11.8%; calculated: C,58.45; H,4.91; N,12.03%];
N-(3,5-difluoropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
(after flash chromatography on alumina, using a mixture of pentane and ethyl acetate (9:1 v/v) as eluent) 6-cyclopentyloxy-N-(3,5-dichloropyrid-4-yl)-5-methoxypyridine-2-carboxamide, in the form of a white solid, m.p. 164-166°C. [Elemental analysis: C,53.6; H,4.56; Cl,18.4; N,11.2%; calculated: C,53.4; H,4.48; Cl,18.55; N,10.99%]; and
N-(3,5-dichloropyrid-4-yl)-5-methoxy-6-(tetrahydro-3-furyloxy)pyridine-2-carboxamide.

EXAMPLE 82 Compounds KK-KL

Thionyl chloride (0.46 mL) is added to a solution of 5-cyclopentyloxy-6-methoxynicotinic acid (500 mg; that is prepared as in Reference Example 48) and dimethylformamide (1 drop) in toluene (10 mL). The mixture is heated and stirred at reflux for 1 hour. The mixture is cooled and concentrated, and the

- residue is dissolved in dichloromethane (5 mL). This solution is added dropwise to a solution of 4-amino-3,5-dimethyl- isoxazole (168 mg) and triethylamine (0.21 mL) in dichloromethane (20 mL). The resulting mixture is stirred at room temperature for 2 hours then at reflux for 1 hour. The cooled mixture is washed with water, with aqueous hydrochloric acid (2 M), and with water, and then dried over magnesium sulphate. After concentration, the yellow oily residue is triturated with a mixture of n-pentane and methyl tert-butyl ether to give 5-cyclopentyloxy-N-(3,5-dimethylisoxazol-4-yl)-6-methoxynicotinamide (240 mg) in the form of a buff solid, m.p. 139-40°C.
- 5
- 10 [Elemental analysis: C,61.3; H,6.40; N,12.4%; calculated: C,61.6; H,6.39; N,12.68%].

- By proceeding in a similar manner, but using 6-methoxy-5-(tetrahydro-3-furyloxy)nicotinic acid instead of 5-cyclopentyloxy-6-methoxynicotinic acid, there is prepared N-(3,5-dimethylisoxazol-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide.
- 15

EXAMPLE 83 Compounds KM-KN

- A solution of n-butyl lithium in hexanes (4.9 mL; 2.5 M) is added, dropwise, to a stirred solution of diisopropylamine (1.7 mL) in dry tetrahydrofuran (20 mL) at -78°C under a nitrogen atmosphere. After 30 minutes, a solution of 3,5-dichloro-4-methylpyridine (1.95 g) in dry tetrahydrofuran (10 mL) is added, dropwise, and the solution is stirred at -78°C for a further 30 minutes. A solution of methyl 5-cyclopentyloxy-6-methoxynicotinate (1.5 g; that is prepared as in Reference Example 48) in dry tetrahydrofuran (15 mL) is added and the red mixture is stirred and allowed to warm to room temperature during 4 hours. The mixture is stirred at room temperature overnight, and then it is treated with a saturated aqueous solution of ammonium chloride. The tetrahydrofuran layer is separated and the aqueous phase is extracted with ethyl acetate. The combined organic layers are washed with brine and dried over anhydrous magnesium sulphate.
- 20
- 25
- 30
- 35
- Concentration gives a light brown oil, which is triturated with a mixture of n-pentane and methyl tert-butyl ether, to give 1-(5-cyclopentyloxy-6-methoxypyrid-3-yl)-2-(3,5-dichloropyrid-4-yl)ethanone (1.0 g) in the form of a beige solid, m.p. 118-119°C. [Elemental analysis: C,56.8; H,4.82; Cl,18.5; N,7.40%; calculated: C,56.7; H,4.76; Cl,18.6; N,7.35%].
- By proceeding in a similar manner, but using 6-methoxy-5-(tetrahydro-3-furyloxy)nicotinic acid (that is prepared as in Reference Example 115) instead

of 5-cyclopentyloxy-6-methoxynicotinic acid, there is prepared 2-(3,5-dichloropyrid-4-yl)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone.

EXAMPLE 84 Compounds KO-KV

- By the application or adaption of known methods, for example methods described hereinbefore or methods similar to those described hereinbefore, there are prepared:-
- 5 N-(3,5-dichloropyrid-4-yl)-5-cyclopentyloxy-6-(methylthio)nicotinamide, m.p. 144-145°C, using the product of Reference Example 48 under conditions as in Example 80;
- 10 1-(5-cyclopentyloxy-6-methoxypyrid-3-yl)-2-(3,5-dichloro-1-oxido-4-pyridinio)ethanone (hemihydrate), m.p. 171-172°C, using the product of Example 83 under conditions as in Example 68;
- 15 N-(3,5-dichloropyrid-4-yl)-5-isopropoxy-6-(methylthio)nicotinamide, m.p. 167-168°C, using the product of Reference Example 48 under conditions as in Example 80;
- 20 1-[5-isopropoxy-6-(methylthio)pyrid-3-yl]-2-(3,5-dichloropyrid-4-yl)ethanone, m.p. 124-125°C, using the product of Reference Example 47 under conditions as in Example 83;
- 25 N-(3,5-dichloropyrid-4-yl)-6-(methylthio)-5-(tetrahydro-3-furyloxy)nicotinamide, using the product of Reference Example 115 under conditions as in Example 80;
- 30 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone, using the product of Example 83 under conditions as in Example 68;
- 25 N-(3,5-dichloropyrid-4-yl)-5-(1-methoxy-2-propoxy)-6-(methylthio)nicotinamide, using the product of Reference Example 115 under conditions as in Example 80; and
- 30 2-(3,5-dichloropyrid-4-yl)-1-[5-(1-methoxy-2-propoxy)-6-(methylthio)pyrid-3-yl]-ethanone, using the esterified product of Reference Example 116 under conditions as in Example 80.

EXAMPLE 85 Compounds ZA, ZB, DW and ZD

By proceeding in a similar manner to Example 1, but replacing the (±)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride with the appropriate quantities of (S)-(+)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride,

5 (R)-(-)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride,

(±)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzoyl chloride, and

(±)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carbonyl chloride,

respectively, there were prepared:-

(S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-

10 benzamide, m.p. 159-161°C. specific rotation [25°C, Na D line] = (+) 9.78°.

[Elemental analysis: C, 52.6; H, 4.2; N, 7.1; calculated: C, 52.6; H, 4.2; N, 7.2%],

(R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-

benzamide, m.p. 159-161°C. specific rotation [25°C, Na D line] = (-) 5.33°.

[Elemental analysis: C, 52.5; H, 4.3; N, 7.2; calculated: C, 52.6; H, 4.2; N, 7.2%],

15 (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(1-methoxyprop-2-yloxy)-

benzamide [Elemental analysis: C, 52.7; H, 4.8; N, 7.1; calculated: C, 53.0; H, 4.7; N, 7.3%], and

(±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-

pyridinecarboxamide (0.98 g), m.p. 146-147°C. [Elemental analysis: C, 50.0;

20 H, 4.0; Cl, 18.4; N, 10.9; calculated: C, 50.0; H, 3.9; Cl, 18.5; N, 10.9%].

EXAMPLE 86 Compound ZC

By proceeding in a similar manner to Example 2 but replacing the (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide with the appropriate quantity of (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(1-

25 methoxyprop-2-yloxy)benzamide, there was prepared (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide

hemihydrate [Elemental analysis: C, 49.6; H, 4.4; N, 6.65; calculated: C, 49.8; H, 4.7; N, 6.8%]

EXAMPLE 87 Compounds JH and ZI

30 A stirred solution of diisopropylamine (1.22 ml) in dry tetrahydrofuran (15 ml) was treated with a solution of n-butyl lithium in hexanes (5.1 ml; 1.6 M), under nitrogen, and the solution was stirred at -75°C, and then allowed to warm to room temperature. The mixture was stirred at this temperature for 0.5 hours, cooled to -75°C, and treated dropwise with a solution of 3,5-dichloro-4-

35 methylpyridine (1.32 g) in dry tetrahydrofuran (15 ml) and stirred for a further 0.5 hours. It was then treated with a solution of methyl (±)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate (1.17 g) in dry tetrahydrofuran (15 ml),

dropwise at -75°C, and the resulting solution was allowed to warm slowly to room temperature, and then it was stirred overnight. The reaction mixture was then treated with water (1 ml), and then it was concentrated in vacuo and the resulting residue was partitioned between brine (20 ml) and ethyl acetate (20 ml). The organic layer was separated, washed with brine (20 ml), dried (MgSO₄) and concentrated, to give an oil. It was then subjected to mplc on silica gel, using ether as eluent, to give (±)-2-(3,5-dichloropyrid-4-yl)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone (1.2 g). [Elemental analysis: C, 51.5; H, 3.8; N, 3.4; calculated: C, 51.7; H, 3.6; N, 3.35%].

By proceeding in a similar manner, but replacing the (±)-methyl 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate with the appropriate quantity of methyl (±)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carboxylate, there was prepared (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone, m.p. 152-154°C. [Elemental analysis: C, 53.2; H, 4.1; N, 7.3; Cl, 18.4; calculated: C, 53.3; H, 4.2; N, 7.3; Cl, 18.5%].

EXAMPLE 88 Compounds JJ and ZJ

A stirred solution of (±)-2-(3,5-dichloropyrid-4-yl)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone (1.2 g) in dichloromethane (50 ml) at room temperature was treated with 3-chloroperoxybenzoic acid (3.63g;60%) and the solution was heated at reflux for 5 hours. After cooling, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution (30 ml) followed by brine (30 ml). The organic solution was dried (MgSO₄) and evaporated to give a yellow oil. It was then subjected to mplc on silica gel, using a mixture of ethyl acetate and methanol (9:1/v/v) as eluent, to give (±)-2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone (0.82 g), m.p. 192-193°C. [Elemental analysis: C, 49.8; H, 3.5; Cl, 16.3; N, 3.2; calculated: C, 49.8; H, 3.5; Cl, 16.3; N, 3.25].

By proceeding in a similar manner, but replacing the (±)-2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone by the appropriate quantity of (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone, there was prepared (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone, m.p. 223-225°C. [Elemental analysis: C, 51.3; H, 4.1; N, 7.0; Cl, 17.7; calculated: C, 51.5; H, 4.0; N, 7.0; Cl, 17.8%].

EXAMPLE 89 Compound ZE

A stirred solution of 4-acetylamino-3,5-dichloropyridine-1-oxide (1.11 g) in dry dimethylformamide (30 ml) at room temperature under nitrogen, was

treated portionwise with a 60% dispersion in oil of sodium hydride (0.6 g) and the mixture was stirred for a further 3 hours. It was then treated with a solution of (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carbonyl chloride (1.29 g) in dimethylformamide (10 ml), dropwise, and the reaction mixture was stirred overnight. After cooling in an ice-bath, it was treated with piperidine (1.48 ml), dropwise, and the solution was stirred for 4 hours with slow warming to room temperature. After concentration the residue was dissolved in methanol (10 ml) and dry-loaded on to a mpc silica gel column. Elution with a mixture of dichloromethane and methanol (9:1v/v) gave (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (0.06 g), m.p. 201-202°C. [Elemental analysis: C, 47.8; H, 3.8; N, 10.2; calculated: C, 48.1; H, 3.9; N, 10.7%].

EXAMPLE 90 Compound ZF

A stirred solution of (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (0.66 g) in dichloromethane (6 ml) at room temperature under nitrogen was treated with diphosphorus tetraiodide (0.23 g) in one portion. After stirring for 10 minutes, the solution was treated with aqueous sodium sulphite (10 ml) and made alkaline by treatment with aqueous sodium hydroxide solution (30%). The organic layer was separated, dried (MgSO_4) and concentrated. The residue was subjected to mpc on silica gel, eluting with ethyl acetate, to give (\pm)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (0.26 g), m.p. 203-204°C. [Elemental analysis: C, 48.1; H, 3.8; Cl, 17.7; N, 10.4; calculated: C, 48.0; H, 3.8; N, 17.7; N, 10.4%].

EXAMPLE 91 Compound ZG

A stirred solution of (\pm)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (1.0 g) in dichloromethane (100 ml) was treated with 3-chloroperoxybenzoic acid (3.28g;60%) and the solution was heated at reflux for 24 hours. After cooling, the solution was washed with saturated aqueous sodium bicarbonate solution (30 ml) and then with brine (30 ml), dried (MgSO_4) and concentrated. The residue was subjected to mpc on silica gel, eluting with a mixture of ethyl acetate and methanol (19:1v/v), to give (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (0.66 g), m.p. 168-170°C. [Elemental analysis: C, 45.3; H, 3.9; N, 9.45; calculated: C, 46.2; H, 3.6; N, 10.1%].

EXAMPLE 92 Compound ZH

- By proceeding in a similar manner to Example 1, but replacing the (\pm)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride and 4-amino-3,5-dichloroaminopyridine with the appropriate quantities of (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carbonyl chloride and 4-amino-3,5-difluoroaminopyridine, there was prepared (\pm)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide (0.4 g), m.p. 119-120°C. [Elemental analysis: C, 54.9; H, 4.45; N, 11.9; calculated: C, 54.7; H, 4.3; N, 12.0%].
- 5.

REFERENCE EXAMPLE 1

A stirred solution of 3-hydroxy-4-methoxybenzaldehyde (2.00 g) in dry dimethylformamide (20 mL) is treated portionwise with sodium hydride (60% dispersion in oil; 0.56 g) and the mixture is then heated for 1 hour at 50°C. It is then treated dropwise with cyclopentyl bromide (2.36 g) and is stirred and heated at 50°C for 22 hours. The solution is diluted with water (100 mL) and extracted with diethyl ether (2 x 100 mL). The ethereal extracts are combined, dried over magnesium sulfate and concentrated, to give 3-cyclopentyloxy-4-methoxybenzaldehyde (1.65 g) in the form of a golden oil.

By proceeding in a similar manner, but using the appropriate quantities of cyclohexyl bromide, butyl bromide, propyl bromide, 4-chlorotetrahydropyran, 2-chloroethyl ether and 2-methoxyethyl chloride respectively, there are prepared:

3-cyclohexyloxy-4-methoxybenzaldehyde in the form of a golden oil [Elemental analysis: C,71.8; H,7.8%; Calculated: C,71.8; H,7.7%];

3-butoxy-4-methoxybenzaldehyde in the form of a light brown oil [NMR(CDCl₃): 1.0(t,3H), 1.5(m,2H), 1.9(m,2H), 3.96(s,3H), 4.1(t,2H), 6.96(d,1H), 7.4(m,2H), 9.8(s,1H)];

3-propoxy-4-methoxybenzaldehyde [NMR(CDCl₃): 9.85(s,1H), 7.4(dd,1H), 7.4(d,1H), 7.0(d,1H), 4.05(t,2H), 4.0(s,3H), 1.9(m,2H), 1.06(t,3H)];

4-methoxy-3-(tetrahydro-4-pyranyloxy)benzaldehyde;

4-methoxy-3-(2-ethoxyethoxy)benzaldehyde; and

4-methoxy-3-(2-methoxyethoxy)benzaldehyde.

REFERENCE EXAMPLE 2

A stirred saturated aqueous solution of potassium permanganate (100 mL) is treated with 3-cyclopentyloxy-4-methoxybenzaldehyde (7.4 g; that is prepared as described hereinbefore in Reference Example 1) and sodium carbonate (3.4 g) and the mixture is stirred at 50°C for 1 hour, and then cooled to room temperature. The reaction mixture is acidified by treatment with concentrated hydrochloric acid and then it is treated with aqueous sodium bisulfite solution until a colorless solution is obtained. The reaction mixture is extracted with dichloromethane (2 x 100 mL) and the organic extracts are dried over magnesium sulfate and concentrated. The resulting residue is recrystallized from diethyl ether, to give 3-cyclopentyloxy-4-methoxybenzoic acid (4.78 g) in the form of white crystals. [NMR(CDCl₃): 1.7(s,2H), 1.8-2.2(m,6H), 3.95(s,3H), 4.85(s,1H), 6.9(bs,1H), 7.6(bs,1H), 7.8(s,1H), 9.8(s,1H); Elemental analysis: C,65.6; H,6.8%; Calculated: C,66.1; H,6.8%].

By proceeding in a similar manner, but using the appropriate quantities of the corresponding benzaldehyde derivatives, prepared as described hereinbefore in Reference Example 1, there are prepared:-

3-cyclohexyloxy-4-methoxybenzoic acid in the form of a white solid, m.p. 158-160°C [NMR(CDCl₃): 1.2-2.1 (m,10H),3.94(s,3H),4.3(m,1H),6.9(d,1H), 7.6(s,1H), 7.75 (d,1H)];

3-butoxy-4-methoxybenzoic acid in the form of a white solid, m.p. 130-132°C [NMR(CDCl₃): 1.0 (t,3H), 1.5 (m,2H),1.85(m,2H),3.95(s,3H),4.1(t,2H), 6.92(d,2H),7.6 (s,1H),7.75(d,1H)];

3-propoxy-4-methoxybenzoic acid [(NMR(CDCl₃): 7.76 (dd,1H),7.6(d,1H), 6.9(d,1H),4.04(t,2H),3.94(s,3H),1.9 (m,2H),1.05(t,3H)];

4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoic acid;

4-methoxy-3-(2-ethoxyethoxy)benzoic acid; and

4-methoxy-3-(2-methoxyethoxy)benzoic acid.

1 5 REFERENCE EXAMPLE 3

Stirring thionyl chloride (20 mL) is treated portionwise with 3-cyclopentyloxy-4-methoxybenzoic acid (5.0 g; that is prepared as described hereinbefore in Reference Example 2) and the solution is then heated at 85°C for 3 hours. Toluene (50 mL) is added and the mixture is concentrated to give

2 0 3-cyclopentyloxy-4-methoxybenzoyl chloride (4.12 g) in the form of an oil which slowly crystallized. [NMR(CDCl₃): 1.6-1.7 (m,2H),1.8-1.95(m,4H),1.94-2.05(m,2H),3.94(s,3H),4.85 (m,1H),6.9(d,1H),7.55(d,1H),7.8(q,1H); Elemental analysis: C,61.3; H,5.94; Cl,13.9%; Calculated: C,61.3; H,5.94; Cl,13.92%].

2 5 By proceeding in a similar manner, but using the appropriate quantities of the corresponding benzoic acid derivatives, that are prepared as described hereinbefore in Reference Example 2, there are prepared:

3-cyclohexyloxy-4-methoxybenzoyl chloride in the form of a colorless solid;

3-butoxy-4-methoxybenzoyl chloride in the form of a light brown oil;

3 0 3-propoxy-4-methoxybenzoyl chloride [(NMR(CDCl₃): 7.82 (dd,1H),7.53(d,1H), 6.92(d,1H),4.03(t,2H),3.96(s,3H),1.89 (m,2H),1.06(t,3H)];

4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoyl chloride;

4-methoxy-3-(2-ethoxyethoxy)benzoyl chloride; and

4-methoxy-3-(2-methoxyethoxy)benzoyl chloride.

REFERENCE EXAMPLE 4

3 5 A stirred solution of 4-aminopyridine (40 g) in concentrated hydrochloric acid (500 mL) at 80°C is treated dropwise with aqueous hydrogen peroxide solution (200 mL; 15% w/w), while keeping the temperature between 80°C and

85°C. The solution is then cooled and basified by dropwise treatment with aqueous sodium hydroxide solution (50% w/w), while keeping the temperature below 15°C. The resulting white flocculent precipitate is recrystallized from toluene, to give 4-amino-3,5-dichloropyridine (61.5 g), m.p. 161.5-162.5°C.

5. REFERENCE EXAMPLE 5

A solution of 4-aminopyridine (47 g) in concentrated hydrochloric acid (355 mL) is treated portionwise at 80°C with an aqueous solution of sodium hypochlorite (550 mL; 15% w/v). The mixture is cooled to 30°C and basified by treatment with aqueous sodium hydroxide solution (300 mL; 35% w/v) during 20 minutes. The mixture is stirred and cooled for a further 30 minutes and then it is filtered. The solid is washed well with water and dried at 60°C to give 4-amino-3,5-dichloropyridine (69.5 g).

REFERENCE EXAMPLE 6

A solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (66 g) and sulfamic acid (39.6 g) in glacial acetic acid (500 mL) is treated dropwise during 1 hour with a solution of sodium chlorite (35 g) in water (150 mL). The mixture is stirred at 20°C during 1 hour and then it is treated with water (500 mL) dropwise during 30 minutes. The resulting solid is filtered, washed with water and dried, to give 3-cyclopentyloxy-4-methoxybenzoic acid (60.9 g) in the form of white crystals [Elemental analysis: C,65.8; H,6.7%; calculated: C,66.1; H,6.8%].

By proceeding in a similar manner, but using the appropriate quantities of the corresponding benzaldehyde derivatives, prepared as described hereinbefore in Reference Example 1, there are prepared:-

4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoic acid;
4-methoxy-3-(2-ethoxyethoxy)benzoic acid; and
4-methoxy-3-(2-methoxyethoxy)benzoic acid.

REFERENCE EXAMPLE 7

A solution of triphenylphosphine (17.5 g) in dry tetrahydrofuran (50 mL) under nitrogen is treated with a solution of diisopropyl azodicarboxylate (13.5 g) in dry tetrahydrofuran (50 mL). The solution is stirred is treated with a solution of endo-8,9,10-trinorborneol (5.0 g) in dry tetrahydrofuran (50 mL) followed by a solution of 3-hydroxy-4-methoxybenzaldehyde (10.2 g) in dry tetrahydrofuran (50 mL). The solution is heated at reflux for 15 hours, cooled, poured into water (600 mL), and extracted with diethyl ether (300 mL). The extract is washed with water (100 mL), with aqueous sodium hydroxide solution (2 x 100 mL; 1 M) and with water (2 x 100 mL), dried over magnesium

sulfate and evaporated, to give an oil, which is subjected to flash chromatography on silica gel, eluting with a mixture of pentane and ethyl acetate (95:5 v/v) to give 3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzaldehyde (8.2 g), m.p. 56-61°C.

5 REFERENCE EXAMPLE 8

A stirred suspension of 3-hydroxy-4-methoxybenzaldehyde (50 g) in water (200 mL) at between 0 and 5°C is treated dropwise with an aqueous solution of sodium hydroxide (200 mL; 20% w/v), followed at between 0 and 5°C by benzoyl chloride (38 mL). The reaction mixture is stirred at between 0 and 5°C for 1 hour and then it is allowed to warm to room temperature and is stirred for a further period of 2 hours. The resulting solution is extracted with dichloromethane (2 x 200 mL) and the combined extract is washed with water (200 mL), dried over magnesium sulfate and concentrated, to give 2-methoxy-5-formylphenyl benzoate (35.2 g), m.p. 70-72°C.

1 5 REFERENCE EXAMPLE 9

A stirred solution of potassium permanganate (28 g) in acetone (200 mL) is treated with 2-methoxy-5-formylphenyl benzoate (35.2 g; that is prepared as described in Reference Example 8), and the resulting vigorously reacting mixture is cooled in an ice bath. It is then stirred at room temperature for 3 hours. The mixture is then concentrated and the residue is treated with saturated aqueous sodium metabisulfite solution (300 mL). The resulting white solid is filtered off, washed well with water (200 mL), and dried, to give 3-benzoyloxy-4-methoxybenzoic acid (29.3 g), m.p. 180-183°C.

2 0 REFERENCE EXAMPLE 10

2 5 A solution of 3-benzoyloxy-4-methoxybenzoic acid (29.3 g; that is prepared as described in Reference Example 9) in toluene (300 mL) is treated with thionyl chloride (30 mL) and heated on the steam bath for 6 hours. It is then cooled, filtered and concentrated, to give 3-benzoyloxy-4-methoxybenzoyl chloride (28.7 g), m.p. 120-122°C.

3 0 REFERENCE EXAMPLE 11

By proceeding in a manner similar to that described in Example 8, but using 3-benzoyloxy-4-methoxybenzoyl chloride (that is prepared as described in Reference Example 10) and 4-amino-3,5-dichloropyridine (that is prepared as described in Reference Example 4) as starting materials, there is prepared 3 5 N-(3,5-dichloropyrid-4-yl)-3-benzoyloxy-4-methoxybenzamide, m.p. 191-192°C.

REFERENCE EXAMPLE 12

A solution of N-(3,5-dichloropyrid-4-yl)-3-benzoyloxy-4-methoxybenzamide (13.4 g; that is prepared as described in Reference Example 11) in methanol (160 mL) and water (60 mL) is treated with anhydrous potassium carbonate (18 g), and stirred overnight at room temperature. It is then brought to pH 7 by treatment with dilute hydrochloric acid (2 N), and concentrated. The residue is treated with water (100 mL) and filtered, and the resulting solid is dried, to give N-(3,5-dichloropyrid-4-yl)-3-hydroxy-4-methoxybenzamide (8.8 g), m.p. 227-228°C.

REFERENCE EXAMPLE 13

By proceeding in a manner similar to that described in Reference Example 2, but using the appropriate quantities of 3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzaldehyde (that is prepared as described in Reference Example 7) and (R)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzaldehyde and (S)-3-(exo-8,9,10-trinorbornyl-2-oxy)-4-methoxybenzaldehyde [that are similarly prepared from (R)-endo-8,9,10-trinorborneol and (S)-endo-8,9,10-trinorborneol or as described in the specification of European Patent Publication No. 0428302A2] there are prepared:

3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoic acid, m.p. 155-156°C;
(R)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoic acid, m.p. 155-156°C;
and
(S)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoic acid, m.p. 155-156°C.

REFERENCE EXAMPLE 14

By proceeding in a manner similar to that described in Reference Example 3, but using the appropriate quantities of the corresponding benzoic acid derivatives (that are prepared as described hereinbefore in Reference Example 13) there are prepared:

3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoyl chloride;
(R)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoyl chloride; and
(S)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-methoxybenzoyl chloride; each in the form of oils.

REFERENCE EXAMPLE 15

A solution of methyl 4-chloro-3-nitrobenzoate (28 g) in acetone (250 mL) is treated portionwise with sodium thiomethoxide (10 g) and the mixture is stirred overnight at room temperature. After filtration, the solution is concentrated and water (300 mL) is added to the residue. The yellow solid is filtered off and subjected to flash chromatography eluting with a mixture of

diethyl ether and pentane (1:4 v/v), to give methyl 4-methylthio-3-nitrobenzoate (18.5 g), in the form of a yellow solid, m.p. 118-120°C.

REFERENCE EXAMPLE 16

- 5 A stirred solution of methyl 4-methylthio-3-nitrobenzoate (6.82 g) in methanol (350 mL) is hydrogenated using a 5% w/w palladium on charcoal catalyst (0.8 g) at room temperature for 48 hours. After filtration the solution is concentrated, to give methyl 3-amino-4-(methylthio)benzoate (3.5 g), in the form of a pale yellow solid m.p. 63-65°C.

REFERENCE EXAMPLE 17

- 10 A stirred solution of concentrated hydrochloric acid (3.2 mL) in water (3.6 mL) at from 0°C to 5°C is treated with methyl 3-amino-4-(methylthio)-benzoate (1.97 g), followed by a solution of sodium nitrite (0.82 g) in water (2 mL), at such a rate that the temperature remained from 0°C to 5°C. The mixture is then allowed to warm to room temperature and it is stirred for a further period
15 of 1 hour. The reaction mixture is treated with water (30 mL) and then heated to 55-60°C, until the evolution of nitrogen ceased (4 hours). The mixture is extracted with dichloromethane (2 x 100 mL) and the combined organic extracts are dried and concentrated. The resulting brown oil is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:4
20 v/v), to give methyl 3-hydroxy-4-(methylthio)benzoate (0.6 g) in the form of a yellow solid.

REFERENCE EXAMPLE 18

- A stirred solution of methyl 3-hydroxy-4(methylthio)benzoate (1.98 g) in dry dimethylformamide (40 mL) is treated with sodium hydride (0.44 g; 60%
25 dispersion in mineral oil; 11 mmol) and the solution is stirred for a further 25 minutes. The reaction mixture is treated with cyclopentyl bromide (1.64 g), stirred at 60°C for 3 hours, and then concentrated. The resulting residue is partitioned between dichloromethane (50 mL) and water (50 mL), the aqueous layer is extracted with dichloromethane (50 mL), and the combined organic
30 layers are dried and concentrated, to give a red oil. The oil is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:9 v/v), to give methyl 3-cyclopentyloxy-4-(methylthio)benzoate (1.9 g), m.p. 53-55°C.

- By proceeding in a similar manner, but using the appropriate quantities of 4-chlorotetrahydropyran, 2-chloroethyl ether and 2-methoxyethyl chloride
35 respectively, there are prepared:

methyl 4-(methylthio)-3-(tetrahydro-4-pyranyloxy)benzoate;
methyl 4-(methylthio)-3-(2-ethoxyethoxy)benzoate; and

methyl 4-(methylthio)-3-(2-methoxyethoxy)benzoate.

REFERENCE EXAMPLE 19

A suspension of methyl 3-cyclopentyloxy-4-(methylthio)benzoate (0.8 g) in methanol (10 mL) and water (5 mL) is treated with potassium carbonate (0.48 g) and the mixture is heated at reflux for 7 hours. The mixture is concentrated, and the resulting residue is partitioned between diethyl ether (20 mL) and water (20 mL). The aqueous layer is separated, acidified to pH 1 by treatment with dilute hydrochloric acid (2 N), and extracted with dichloromethane (2 x 25 mL). The combined organic extracts are dried and concentrated, to give 3-cyclopentyloxy-4-(methylthio)benzoic acid (0.7 g) in the form of a white solid m.p. 150-152°C.

By proceeding in a similar manner, but using the appropriate quantities of esters respectively, there are prepared:

- 4-(methylthio)-3-(tetrahydro-4-pyranyloxy)benzoic acid;
- 4-(methylthio)-3-(2-ethoxyethoxy)benzoic acid; and
- 4-(methylthio)-3-(2-methoxyethoxy)benzoic acid.

REFERENCE EXAMPLE 20

3-Cyclopentyloxy-4-(methylthio)benzoic acid (0.7 g) is dissolved in toluene (20 mL) and heated at 80°C for 1 hour 30 minutes in the presence of thionyl chloride (5 mL). The reaction mixture is concentrated to give 3-cyclopentyloxy-4-(methylthio)benzoyl chloride (0.76 g), in the form of a yellow oil.

By proceeding in a similar manner, but using the appropriate quantities of acids respectively, there are prepared:

- 4-(methylthio)-3-(tetrahydro-4-pyranyloxy)benzoyl chloride;
- 4-(methylthio)-3-(2-ethoxyethoxy)benzoyl chloride; and
- 4-(methylthio)-3-(2-methoxyethoxy)benzoyl chloride.

REFERENCE EXAMPLE 21

A cold (0°C) solution of diisopropyl azodicarboxylate (5.1 g) in dry tetrahydrofuran (10 mL) is treated with a solution of triphenylphosphine (6.6 g) in dry tetrahydrofuran (10 mL). The resulting creamy precipitate is stirred in the cold for a further 0.5 hours, and treated with a solution of endo-8,9,10-trinorborneol (1.4 g) in dry tetrahydrofuran (10 mL), followed by a solution of methyl 3-hydroxy-4-(methylthio)benzoate (5.0 g) in dry tetrahydrofuran (10 mL) (that is prepared as described in Reference Example 17). The resulting mixture is then heated at reflux for 17 hours, cooled, poured into water (300 mL) and extracted with diethylether (2 x 250 mL). The combined ethereal

extracts are dried over sodium sulfate and evaporated under reduced pressure to give an oil, which is subjected to flash chromatography on silica gel with dichloromethane/pentane (gradient elution 1:4 v/v to 3:1 v/v) to give methyl 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoate (3.0 g) as a colorless oil.

By proceeding in a similar manner, but replacing (endo)-8,9,10-trinorborneol used as starting material by the appropriate quantities of (R)-(endo)-8,9,10-trinorborneol and (S)-(endo)-8,9,10-trinorborneol [that are prepared as described in European Patent Publication No. 0 428 302 A2] there are prepared:

(R)-methyl 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoate, m.p. 63-64°C (from heptane), $[\alpha]_D^{22} -12.9^\circ$ (c=0.72, CH₂Cl₂); and

(S)-methyl 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoate, m.p. 65-66°C (from heptane), $[\alpha]_D^{22} +31.5^\circ$ (c=1.20, CH₂Cl₂).

By proceeding in a similar manner, but replacing (endo)-8,9,10-trinorborneol used as starting material by the appropriate quantities of cyclopentanol, 3-hydroxytetrahydrofuran, 7-oxabicyclo[2.2.1]heptan-2-ol, (exo)-2-oxabicyclo[2.2.1]heptan-6-ol, (endo)-2-oxabicyclo[2.2.1]heptan-6-ol, 1-methoxyprop-2-ol, 3-methoxybutanol and tetrahydro-4H-pyran-4-ol and/or replacing methyl 5-(hydroxy)-6-(methylthio)benzoate by methyl 5-(hydroxy)-6-(methylthio)nicotinate there are prepared:

methyl 4-(methylthio)-3-(cyclopentyloxy)benzoate;

methyl 4-(methylthio)-3-(tetrahydro-3-furyloxy)benzoate;

methyl 4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoate;

methyl 4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzoate;

methyl 4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzoate;

methyl 3-(1-methoxyprop-2-oxy)-4-(methylthio)benzoate;

methyl 3-(3-methoxybutoxy)-4-(methylthio)benzoate;

methyl 4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)benzoate;

methyl 6-(methylthio)-5-(cyclopentyloxy)nicotinate; and

methyl 6-(methylthio)-5-(tetrahydro-3-furyloxy)nicotinate.

REFERENCE EXAMPLE 22

By proceeding in a manner similar to that described in Reference Example 19, but using the appropriate quantities of esters that are prepared as described in Reference Example 21, there are prepared:

3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoic acid;

(R)-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoic acid, m.p. 151-152°C
(from heptane/toluene), $[\alpha]_D^{22} +10.9^\circ$ (c=0.92, CH₂Cl₂);

(S)-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoic acid, m.p. 167-168°C
(from heptane/toluene), $[\alpha]_D^{20} +23.8^\circ$ (c=1.48, CH₂Cl₂);

- 5 4-(methylthio)-3-(cyclopentyloxy)benzoic acid;
4-(methylthio)-3-(tetrahydro-3-furyloxy)benzoic acid;
4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoic acid;
4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzoic acid;
4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzoic acid;
- 10 3-(1-methoxyprop-2-oxy)-4-(methylthio)benzoic acid;
3-(3-methoxybutoxy)-4-(methylthio)benzoic acid;
4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)benzoic acid;
6-(methylthio)-5-(cyclopentyloxy)nicotinic acid; and
6-(methylthio)-5-(tetrahydro-3-furyloxy)nicotinic acid.

15 REFERENCE EXAMPLE 23

- To 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoic acid (2.7 g),
that is prepared as in Reference Example 22) in dry dichloromethane (30 mL)
is added oxalyl chloride (1.3 mL). The resulting mixture is stirred at room
temperature for 2 hours and then concentrated to give 3-(exo)-8,9,10-
20 trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride as an off yellow oil (2.8 g).

- By proceeding in a similar manner but replacing 3-(exo)-8,9,10-
trinorbornyl-2-oxy-4-(methylthio)benzoic acid used as starting material by the
appropriate quantities of (R)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-
(methylthio)benzoic acid and (S)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-
25 (methylthio)benzoic acid (that are prepared as described in Reference
Example 22) there are prepared:

- (R)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride;
- (S)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-(methylthio)benzoyl chloride;
- 4-(methylthio)-3-(cyclopentyloxy)benzoyl chloride;
- 30 4-(methylthio)-3-(tetrahydro-3-furyloxy)benzoyl chloride;
- 4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoyl chloride;
- 4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzoyl chloride;
- 4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzoyl chloride;
- 3-(1-methoxyprop-2-oxy)-4-(methylthio)benzoyl chloride;
- 35 3-(3-methoxybutoxy)-4-(methylthio)benzoyl chloride;
- 4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)benzoic acid;

6-(methylthio)-5-(cyclopentyloxy)nicotinoyl chloride; and
6-(methylthio)-5-(tetrahydro-3-furyloxy)nicotinoyl chloride.

REFERENCE EXAMPLE 24

- Concentrated sulfuric acid (27.6 g) is slowly added to a stirred
5 suspension of 3-hydroxy-4-nitrobenzoic acid (54.9 g, 0.3 mol) in methanol (135 mL) at ambient temperature. The resulting yellow slurry is stirred at reflux giving a complete solution after 30 minutes and the stirring at reflux is continued for 3 hours. The mixture is allowed to cool then diluted with water (600 mL) and the resulting mixture is then extracted with toluene (2 x 250 mL).
10 The combined organic extract is washed with saturated aqueous sodium hydrogen carbonate solution (1 x 300 mL) and then dried (MgSO_4). The solvent is then removed under reduced pressure to give a yellow solid residue (54.9 g, 92.8%) which is identified as methyl 3-hydroxy-4-nitrobenzoate m.p. 92-94°C. [Elemental analysis: C, 49.1; H, 3.57; N, 7.3%; calculated: C, 48.74; H, 3.58; N, 7.1%].
15

REFERENCE EXAMPLE 25

- Cyclopentyl bromide (20g, 134 mmol) is added slowly (over 30 minutes) to a stirred suspension of potassium carbonate (27.6 g, 200 mmol) in N,N'-dimethylimidazolidinone (75 mL) containing 3-hydroxy-4-nitrobenzoic
20 acid (9.15 g, 50 mmol) at 85°C and then stirring is continued for 14 hours. The mixture is allowed to cool and then filtered. The filtrate is diluted with water (100 mL) then extracted with toluene (2 x 100 mL). The combined organic extract is dried over magnesium sulfate and then the solvent is removed under reduced pressure to give a brown mobile oil. This oil is subjected by flash
25 chromatography on silica gel (dichloromethane as eluent) and the eluent evaporated under reduced pressure to give cyclopentyl 3-cyclopentyloxy-4-nitrobenzoate (10.2 g, 81.6%) as a yellow solid m.p. 45.5 - 46.5°C. [Elemental analysis: C, 63.7; H, 6.66; N, 4.37%; calculated: C, 63.93; H, 6.63; N, 4.39%].

REFERENCE EXAMPLE 26

- Cyclopentyl bromide (38.7 g, 0.26 mol) is added slowly (over 1 hour) to a stirred suspension of potassium carbonate (41.4 g, 0.3 mol) in N,N'-dimethylformamide (200 mL) containing methyl 3-hydroxy-4-nitrobenzoate (39.4 g, 0.2 mol) at 65°C and then the stirring is continued for 4 hours. The mixture is allowed to cool and then filtered. The filtrate is diluted with water
30 (700 mL) containing sodium chloride (50 g) and then extracted with toluene (3 x 200 mL). The combined organic extract is washed with 1N sodium hydroxide solution (1 x 200 mL) and then water (2 x 200 mL) and then evaporated under

reduced pressure to give methyl 3-cyclopentyloxy-4-nitrobenzoate (54.2 g, 100%) as a pale green solid which is used without further purification.

By proceeding in a similar manner, but using the appropriate quantities of 4-chlorotetrahydropyran, 2-chloroethyl ether and 2-methoxyethyl chloride
5 respectively, there are prepared:

methyl 4-nitro-3-(tetrahydro-4-pyranyloxy)benzoate;

methyl 3-(2-ethoxyethoxy)-4-nitrobenzoate; and

methyl 3-(2-methoxyethoxy)-4-nitrobenzoate.

REFERENCE EXAMPLE 27

10 Sodium thiomethoxide (8.05 g, 0.115 mol) is added portionwise to a stirred solution of methyl 3-cyclopentyloxy-4-nitrobenzoate (26.5 g, 0.1 mol) in N,N'-dimethylimidazolidinone (200 mL) at ambient temperature under an atmosphere of nitrogen and stirring continued for 4 hours. The mixture is then
15 diluted with water (1200 mL) containing sodium chloride (200 g) and extracted with ethyl acetate (2 x 300 mL). The combined extract is washed with saturated brine (2 x 300 mL) and then evaporated under reduced pressure to give methyl 3-cyclopentyloxy-4-(methylthio)benzoate (24.4g, 91.7%) as an orange brown solid which is used without further purification.

By proceeding in a similar manner, but using the appropriate quantities
20 of methyl 4-nitrobenzoates of Reference Example 26, there are prepared:
methyl 4-(methylthio)-3-(tetrahydro-4-pyranyloxy)benzoate;
methyl 3-(2-ethoxyethoxy)-4-(methylthio)benzoate; and
methyl 3-(2-methoxyethoxy)-4-(methylthio)benzoate.

REFERENCE EXAMPLE 28

25 Sodium thiomethoxide (0.177 g, 2.5 mmol) is added portionwise to a stirred solution of cyclopentyl 3-cyclopentyloxy-4-nitrobenzoate (0.64 g, 2 mmol) in N,N'-dimethylimidazolidinone (10 mL) at ambient temperature under an atmosphere of nitrogen and stirring continued for 4 hours. The mixture is then diluted with water (100 mL) containing sodium chloride (15 g) and
30 extracted with ethyl acetate (2 x 50 mL). The combined extract is washed with saturated brine (1 x 100 mL) and then dried over magnesium sulfate and evaporated under reduced pressure to give cyclopentyl 3-cyclopentyloxy-4-(methylthio)benzoate (0.52 g, 81%) as a brown viscous oil which is used without further purification.

REFERENCE EXAMPLE 29

Method 1

A solution of methyl 3-cyclopentyloxy-4-(methylthio)benzoate (24.3 g,

91.4 mmol) in water (200 mL) and ethanol (50 mL) containing sodium hydroxide (18.3 g, 460 mmol) is heated under reflux for 3 hours. The solution is then poured into water (750 mL) and 1N acetic acid is added dropwise with stirring to between pH 5-6. The solid which separates is collected by filtration, washed with water (4 x 100 mL) and dried giving 3-cyclopentyloxy-4-(methylthio)benzoic acid (21.1 g, 91.7%) as a cream solid m.p. 158-160°C. [Elemental analysis: C,61.5; H,6.31%; calculated: C,61.88; H,6.39%]

Method 2

A solution of cyclopentyl 3-cyclopentyloxy-4-(methylthio)benzoate (0.5 g, 1.5 mmol) in water (30 mL) and methanol (10 mL) containing sodium hydroxide (1 g, 25 mmol) is heated under reflux for 3 hours. The solution is then poured into water (60 mL) and acetic acid is added dropwise with stirring to between pH 5-6. The solid which separates is collected by filtration, washed with water (5 x 10 mL) and dried giving 3-cyclopentyloxy-4-(methylthio)benzoic acid (0.35 g, 88.6%) as a cream solid m.p. 158-160°C.

By proceeding in a similar manner to either method 1 or 2, but using the appropriate quantities of methyl 4-(methylthio)benzoates of Reference Example 27, there are prepared:

- 4-(methylthio)-3-(tetrahydro-4-pyranyloxy)benzoic acid;
- 3-(2-ethoxyethoxy)-4-(methylthio)benzoic acid; and
- 3-(2-methoxyethoxy)-4-(methylthio)benzoic acid.

REFERENCE EXAMPLE 30

A solution of 3-hydroxy-4-methoxybenzaldehyde (14.20 g) in dry dimethylformamide (300 mL) is treated portionwise with sodium hydride (60% dispersion in oil; 3.70 g) at room temperature under nitrogen. 3-Chlorocyclopentene (9.6 mL) is added and the resulting mixture is stirred overnight. The solvent is then removed under reduced pressure and the residue is partitioned between water (500 mL) and dichloromethane (500 mL) and the aqueous layer is further extracted with dichloromethane (500 mL). The combined organic extracts are dried and evaporated under reduced pressure and the residue is subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate and pentane (1:1 v/v), to give 3-cyclopent-2-enyloxy-4-methoxybenzaldehyde, in the form of a pale brown oil (11.2 g).

REFERENCE EXAMPLE 31

A solution of 3-cyclopent-2-enyloxy-4-methoxybenzaldehyde (7.70 g) in t-butanol (160 mL) and 2-methyl-2-butene (40 mL) is treated dropwise with an aqueous solution (150 mL) containing sodium chlorite (80% technical grade;

- 4.39 g) and sodium dihydrogen phosphate (38.49 g), and left to stand overnight. The resulting mixture is extracted with dichloromethane (2 x 250 mL), and the combined organic layers are dried over sodium sulfate, the solvent is removed under reduced pressure, and the resulting residue is
- 5 recrystallized from ethyl acetate, to give 3-cyclopent-2-enyloxy-4-methoxybenzoic acid (5.89 g), in the form of a colorless solid. m.p. 160-163°C. [Elemental analysis: C,66.4; H,6.0%; calculated: C,66.7; H,6.0%].

REFERENCE EXAMPLE 32

- A solution of 3-cyclopent-2-enyloxy-4-methoxybenzoic acid (5.89 g) in dry
- 10 dichloromethane (50 mL) under nitrogen at room temperature is treated with triethylamine (10.50 mL), followed by oxalyl chloride (2.40 mL). The resulting mixture is stirred for 2.5 hours, then most of the solvent is removed under reduced pressure, and the resulting residue is taken up in dry tetrahydrofuran (50 mL) and filtered through a pad of diatomaceous earth. The resulting
- 15 solution, containing 3-cyclopent-2-enyloxy-4-methoxybenzoyl chloride, is used immediately without further purification.

REFERENCE EXAMPLE 33

- A stirred suspension of sodium hydride (60% in oil, 0.88 g) in dry dimethylformamide (44 mL) under nitrogen at between 5-10°C is treated with a
- 20 solution of 3-hydroxy-4-methoxy benzaldehyde (3.35 g) in dry dimethylformamide (6.3 mL). The resulting mixture is allowed to warm to room temperature and stirred for 40 minutes before recooling to between 5-10°C. A solution of 4-(p-toluenesulfonyl)cyclopentene (5.24 g) in dry dimethylformamide (12.6 mL) is added dropwise maintaining the temperature
- 25 below 10°C. The resulting mixture is allowed to warm to room temperature, left to stand for 46 hours, and then poured into 5% aqueous potassium carbonate (305 mL). t-Butyl methyl ether is added (150 mL), and the layers are thoroughly stirred and separated. The aqueous layer is further extracted with t-butyl methyl ether (2 x 75 mL), the combined organic extracts are washed with
- 30 water (3 x 30 mL) and dried over magnesium sulfate. The solvent is removed under reduced pressure and the resulting residue is subjected to flash chromatography on silica gel, eluting with mixtures of ethyl acetate and pentane (1:10 to 3:10), to give 3-cyclopent-3-enyloxy-4-methoxybenzaldehyde as a pale amber viscous oil that slowly crystallizes on standing (1.75 g).
- 35 Recrystallization of a portion (0.5 g) from cyclohexane gives an analytically pure sample (0.4 g), m.p. 60-62°C [Elemental analysis: C,71.8; H,6.5%; calculated: C,71.5; H,6.8%].

REFERENCE EXAMPLE 34

A stirred solution of 3-cyclopent-3-enyloxy-4-methoxybenzaldehyde (1.75 g) in t-butanol (36.5 mL) and 2-methyl-2-butene (9.0 mL) is treated dropwise with an aqueous solution (34 mL) containing sodium chlorite (80% technical grade; 1.0 g) and sodium dihydrogen phosphate (8.75 g). The resulting mixture is further stirred for 5 hours, the layers are separated and the aqueous layer is extracted with t-butyl methyl ether (3 x 30 mL). The combined organic layers are washed with water (2 x 15 mL), dried over sodium sulfate and the solvent removed under reduced pressure. The resulting residue is recrystallized from ethyl acetate to give 3-cyclopent-3-enyloxy-4-methoxybenzoic acid (1.31 g), in the form of a colorless solid, m.p. 171-173°C [Elemental analysis: C,66.6; H,6.0%; calculated: C,66.7; H,6.0%].

REFERENCE EXAMPLE 35

A solution of 3-cyclopent-3-enyloxy-4-methoxybenzoic acid (1.33 g) in dry tetrahydrofuran (20 mL) under nitrogen at room temperature is treated with triethylamine (2.36 mL), followed by oxalyl chloride (0.70 mL). The resulting mixture is stirred for 1 hour and then filtered through a pad of diatomaceous earth. The solid collected is washed with dry tetrahydrofuran (10 mL). The resulting combined filtrates, containing 3-cyclopent-3-enyloxy-4-methoxybenzoyl chloride, is used immediately without further purification.

REFERENCE EXAMPLE 36

A stirred solution of sodium hydroxide (16.8 g) in water (32 mL) at 20°C is treated with dimethyl sulfoxide (560 mL). It is then treated with 3,4-dihydroxybenzaldehyde (56.9 g), portionwise during 5 minutes, while keeping the temperature at 20°C. It is then treated with benzyl bromide (49.7 mL), portionwise, at 20°C. The solution is then heated at 80°C for 6 hours and then allowed to stand at room temperature overnight. After dilution with ice-water (2240 mL) the solution is extracted with diethyl ether (1 x 1000 mL, 2 x 250 mL). The combined ether extracts are washed with water, dried over magnesium sulfate and concentrated, to give an oily solid, which is recrystallized from a mixture of ethyl acetate and isopropanol, to give 4-benzyloxy-3-hydroxybenzaldehyde (60.9 g), in the form of pale yellow crystals, m.p. 118-120°C.

REFERENCE EXAMPLE 37

A stirred solution of 4-benzyloxy-3-hydroxybenzaldehyde (60.9 g; that is prepared as described in Reference Example 36) in dry dimethylformamide (270 mL) under nitrogen is treated portionwise with potassium carbonate

(79.5 g). After stirring at room temperature for 45 minutes, it is treated with cyclopentyl bromide (34.3 mL), and the resulting suspension is heated at 60°C for 8 hours. After cooling, the solution is evaporated to low bulk under reduced pressure, to give an oil. This oil is treated with water (250 mL) and diethyl ether (300 mL), and the aqueous layer is washed with further quantities of diethyl ether (2 x 50 mL). The combined ethereal extracts are washed with brine (1 x 50 mL) and with water (3 x 50 mL), dried over magnesium sulfate and evaporated. The resulting residue is crystallized from methanol, to give 4-benzyloxy-3-cyclopentyloxybenzaldehyde (79 g), m.p. 55-56°C. [Elemental analysis: C,77.1; H,6.9%; calculated: C,77.0; H,6.8%].

By proceeding as described in Reference Example 21, using 3-hydroxytetrahydrofuran, 1-methoxy-2-propanol and 7-oxabicyclo[2.2.1]heptan-2-ol, there are prepared:

4-benzyloxy-3-(tetrahydro-3-furyloxy)benzaldehyde;

4-benzyloxy-3-(1-methoxy-2-propan-2-oxy)benzaldehyde; and

4-benzyloxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzaldehyde.

REFERENCE EXAMPLE 38

A rapidly stirred solution of 4-benzyloxy-3-cyclopentyloxybenzaldehyde (10.5 g; that is prepared as described in Reference Example 37) in glacial acetic acid (100 mL) is treated with sulfamic acid (4.85 g) and stirred at room temperature for 10 minutes. The solution is then cooled in an ice bath and treated with a solution of sodium chlorite (4.2 g) in water (100 mL) during 15 minutes at 13-15°C. During the addition a white precipitate forms and, because stirring becomes difficult, a further quantity of glacial acetic acid (60 mL) is added. After warming to room temperature, the solution is stirred for a further 6 hours and further quantities of sodium chlorite (1.6 g) and sulfamic acid (1.7 g) are added. The mixture is poured onto water and the resulting solid is filtered off and dried, to give 3-cyclopentyloxy-4-benzyloxybenzoic acid (10 g).

By proceeding in a similar manner using 4-benzyloxybenzaldehydes of Reference Example 37 as the starting materials, there are prepared:

4-benzyloxy-3-(tetrahydro-3-furyloxy)benzoic acid;

4-benzyloxy-3-(1-methoxy-2-propan-2-oxy)benzoic acid; and

4-benzyloxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoic acid.

REFERENCE EXAMPLE 39

A solution of 3-cyclopentyloxy-4-benzyloxybenzoic acid (5.1 g; that is prepared as described in Reference Example 38) in methanol (150 mL) and

concentrated sulfuric acid (1 mL) is heated at reflux for 6 hours, and then it is cooled and concentrated in vacuo. The resulting residue is treated with ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The organic layer is collected, dried and evaporated. The resulting oil is
5 subjected to flash chromatography on silica gel, using a mixture of ethyl acetate and pentane (1:4 v/v) as eluent, to give methyl 3-cyclopentyloxy-4-benzyloxybenzoate (4.8 g), in the form of a white solid, m.p. 58-59°C.

By proceeding in a similar manner using 4-benzyloxybenzoic acids of Reference Example 38 as the starting materials, there are prepared:
10 methyl 4-benzyloxy-3-(tetrahydro-3-furyloxy)benzoate;
methyl 4-benzyloxy-3-(1-methoxy-2-propan-2-oxy)benzoate; and
methyl 4-benzyloxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoate.

REFERENCE EXAMPLE 40

A solution of methyl 3-cyclopentyloxy-4-benzyloxybenzoate (2.64 g; that is
15 prepared as described in Reference Example 39) in methanol (120 mL) is treated with palladium on charcoal (5%, 0.5 g) and ammonium formate (2.0 g) and heated at reflux for 45 minutes. The catalyst is filtered off through a pad of diatomaceous earth and washed with methanol. The filtrate and washings are evaporated under reduced pressure, and the resulting residue is subjected to
20 flash chromatography on silica gel using a mixture of diethyl ether and pentane (1:1 v/v), to give methyl 3-cyclopentyloxy-4-hydroxybenzoate (1.8 g), in the form of a cream solid, m.p. 73-75°C.

By proceeding in a similar manner using 4-benzyloxybenzoates of Reference Example 39 as the starting materials, there are prepared:
25 methyl 4-hydroxy-3-(tetrahydro-3-furyloxy)benzoate;
methyl 4-hydroxy-3-(1-methoxy-2-propan-2-oxy)benzoate; and
methyl 4-hydroxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoate.

REFERENCE EXAMPLE 41

A solution of methyl 3-cyclopentyloxy-4-hydroxybenzoate (0.7 g; that is
30 prepared as described in Reference Example 40) in dimethylformamide (15 mL) is treated with potassium carbonate (0.28 g) and potassium iodide (0.2 g). Chlorodifluoromethane is then bubbled through the reaction mixture at a very slow rate and the reaction mixture is heated at 70-75°C for 5 hours. The mixture is then treated with water (50 mL) and extracted with ethyl acetate (2 x
35 50 mL). The combined ethyl acetate extracts are dried over magnesium sulfate, evaporated under reduced pressure, and subjected to flash chromatography on silica gel using a mixture of diethyl ether and pentane (1:1

v/v), to give methyl 3-cyclopentyloxy-4-difluoromethoxybenzoate, in the form of a pale yellow oil (0.65 g).

By proceeding in a similar manner using 4-hydroxybenzoates of Reference Example 40 as the starting materials, there are prepared:

5. methyl 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate;
methyl 4-difluoromethoxy-3-(1-methoxy-2-propan-2-oxy)benzoate; and
methyl 4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoate.

REFERENCE EXAMPLE 42

- A solution of methyl 3-cyclopentyloxy-4-difluoromethoxybenzoate (0.6 g;
1 0 that is prepared as described in Reference Example 41) in methanol (10 mL) is
treated with potassium carbonate (0.35 g) and water (4 mL), and then it is
heated at reflux for 3 hours. Methanol is evaporated off under reduced
pressure, and the residue is dissolved in water (40 mL). The solution is
washed with diethyl ether (40 mL), acidified with concentrated hydrochloric
1 5 acid, and extracted with ethyl acetate (3 x 40 mL). The combined ethyl acetate
extracts are dried over magnesium sulfate and evaporated under reduced
pressure, to give 3-cyclopentyloxy-4-difluoromethoxybenzoic acid (0.47 g), in
the form of a white solid, m.p. 126-128°C.

- By proceeding in a similar manner using 4-difluoromethoxybenzoates of
2 0 Reference Example 41 as the starting materials, there are prepared:
4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoic acid;
4-difluoromethoxy-3-(1-methoxy-2-propan-2-oxy)benzoic acid; and
4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoic acid.

REFERENCE EXAMPLE 43

- 2 5 A mixture of 3-cyclopentyloxy-4-difluoromethoxybenzoic acid (0.47 g;
that is prepared as described in Reference Example 42) and thionyl chloride (4
mL) in toluene (10 mL) is heated at 80°C for 2 hours, and then evaporated
under reduced pressure, to give 3-cyclopentyloxy-4-difluoromethoxybenzoyl
chloride (0.48 g), in the form of a pale yellow low melting solid, which is used
3 0 without further purification.

- By proceeding in a similar manner using 4-difluoromethoxybenzoic
acids of Reference Example 42 as the starting materials, there are prepared:
4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride;
4-difluoromethoxy-3-(1-methoxy-2-propan-2-oxy)benzoyl chloride; and
3 5 4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzoyl chloride.

REFERENCE EXAMPLE 44

A solution of sodium methoxide in methanol (82.65 mL; 1 M) is added slowly to a stirred solution of methyl 6-chloro-5-nitronicotinate (17 g) in anhydrous methanol (250 mL) and the mixture is stirred for 8 hours. The mixture is concentrated, and the residue is treated with water and extracted with ethyl acetate. The extract is washed with water, treated with decolourising charcoal, and dried over magnesium sulphate. Concentration gives methyl 6-methoxy-5-nitronicotinate (9.8 g), in the form of an orange solid. Recrystallization from cyclohexane gives white needles, m.p. 118-119°C.

By proceeding in a similar manner using sodium thiomethoxide instead of sodium methoxide as the starting material, there is prepared methyl 6-methylthio-5-nitronicotinate.

REFERENCE EXAMPLE 45

A solution of methyl 6-methoxy-5-nitronicotinate (5.4 g) in ethyl acetate (120 mL) is hydrogenated using 5% palladium on carbon (1 g) as catalyst. When hydrogen uptake ceases, the mixture is filtered through a pad of diatomaceous earth and the filtrate is evaporated. The residue is triturated with n-pentane and methyl tert-butyl ether, to give methyl 5-amino-6-methoxynicotinate (4.3 g), in the form of a light-brown solid, m.p. 108-109°C. [Elemental analysis: C, 52.99; H, 5.49; N, 15.25%. calculated: C, 52.74; H, 5.53; N, 15.38%.]

By proceeding in a similar manner using methyl 6-methylthio-5-nitronicotinate instead of methyl 6-methoxy-5-nitronicotinate as the starting material, there is prepared methyl 5-amino-6-(methylthio)nicotinate.

REFERENCE EXAMPLE 46

Concentrated hydrochloric acid (9.06 mL) is added to a stirred suspension of methyl 5-amino-6-methoxynicotinate (3.3 g) in water (20 mL). The mixture is cooled to 0°C and treated dropwise with a solution of sodium nitrite (1.37 g) in water (5 mL). After 30 minutes at 0°C a solution of sodium tetrafluoroborate (2.84g) in water (10 mL) is added. After a further 30 minutes the precipitated diazonium salt is collected, washed with a little ice-cold water, and then with diethyl ether, and sucked dry.

Potassium carbonate (1.0g) is added to trifluoroacetic acid (32 mL) at 0°C, followed by the addition of the diazonium salt, in one portion. The mixture is stirred at reflux for 18 hours, cooled, then poured into iced water and stirred for 1 hour. The aqueous mixture is neutralized by treatment with solid sodium bicarbonate and extracted with ethyl acetate. The extract is washed with water, dried over magnesium sulphate, and concentrated in vacuo, to give methyl

5-hydroxy-6-methoxynicotinate (2.86 g), in the form of a beige solid. This material is used without further purification.

By proceeding in a similar manner using methyl 5-amino-6-(methylthio)nicotinate instead of methyl 5-amino-6-methoxynicotinate as the starting material, there is prepared methyl 5-hydroxy-6-(methylthio)nicotinate.
REFERENCE EXAMPLE 47

A mixture of methyl 5-hydroxy-6-methoxynicotinate (250 mg), anhydrous potassium carbonate (600 mg) and cyclopentyl bromide (0.26 mL) in dry dimethylformamide (5 mL) is stirred and heated at 55-65°C for 24 hours. The mixture is cooled to room temperature, diluted with water and extracted with ethyl acetate. The extract is washed with water, and dried over magnesium sulphate. Concentration in vacuo gives methyl 5-cyclopentyloxy-6-methoxynicotinate (290 mg), in the form of an oil.

By proceeding in a similar manner using methyl 5-hydroxy-6-(methylthio)nicotinate and 3-hydroxytetrahydrofuran or 2-propanol as the starting materials, there are prepared methyl 5-(tetrahydro-3-furyloxy)-6-(methylthio)nicotinate and methyl 6-(methylthio)-5-(2-propoxy)nicotinate.
REFERENCE EXAMPLE 48

A solution of potassium hydroxide (168 mg) in water (1 mL) is added to a solution of methyl 5-cyclopentyloxy-6-methoxynicotinate (250 mg) in methanol (3 mL) and the mixture is stirred for 4 hours, then allowed to stand at room temperature overnight. The mixture is concentrated, the residue is dissolved in water and the mixture is adjusted to pH 6 by the addition of concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the extract is dried over magnesium sulphate and concentrated, to give a cream solid, which is dried at 100°C to give 5-cyclopentyloxy-6-methoxynicotinic acid (140 mg), m.p. 191-192°C. [Elemental analysis: C,60.7; H,6.43; N,5.78%; calculated: C,60.75; H,6.37; N,5.90%].

By proceeding in a similar manner using methyl 5-(tetrahydro-3-furyloxy)-6-(methylthio)nicotinate, there is prepared 5-(tetrahydro-3-furyloxy)-6-(methylthio)nicotinic acid and 6-(methylthio)-5-(2-propoxy)nicotinic acid. These acids are converted to the corresponding acid chlorides and N-methoxy-N-methylbenzamide as in Reference Examples 3 and 64.

REFERENCE EXAMPLE 49

6-Chloro-5-methoxypyridine-2-carbonyl chloride (5.8 g) is added to dry cyclopentanol (50 mL) and the mixture is heated at reflux for 4 hours. The mixture is concentrated, the residue is dissolved in ethyl acetate (400 mL), and

the ethyl acetate solution is washed with water (3x250 mL). After drying over magnesium sulphate the solution is evaporated to dryness, to give cyclopentyl 6-chloro-5-methoxypyridine-2-carboxylate (6.3 g) in the form of a buff solid, m.p. 90-92°C. [Elemental analysis: C,55.9; H,5.47; Cl,13.9; N,5.48%.
5 calculated: C,56.36; H,5.52; Cl,13.8; N,5.48%].

REFERENCE EXAMPLE 50

Sodium hydride (887 mg of a 60% dispersion in oil) is added to a solution of cyclopentanol (3.35 mL) in dry tetrahydrofuran (127 mL) and the mixture is stirred for 90 minutes. Cyclopentyl 6-chloro-5-methoxypyridine-2-carboxylate (6.3 g) is added and the mixture is stirred at room temperature for 21 hours. The mixture is poured into saturated aqueous ammonium chloride solution (500 mL) and the resulting mixture is extracted with ethyl acetate (2x500 mL). The combined extracts are washed with saturated aqueous sodium bicarbonate solution (500 mL) and water (500 mL). After drying over magnesium sulphate the solution is evaporated to dryness, to give a yellow oil which is subjected to flash chromatography on silica gel, using a mixture of pentane and ethyl acetate (9:1 v/v) as eluent, to give cyclopentyl 6-cyclopentyl-10 oxy-5-methoxypyridine-2-carboxylate (3.6 g), in the form of an oil.

Potassium hydroxide (1.98 g) in water (12 mL) is then added to a solution of cyclopentyl 6-cyclopentyl-5-methoxypyridine-2-carboxylate (3.6 g) in methanol (35 mL) and the mixture is stirred at room temperature for 2 hours and 30 minutes. The solution is concentrated to half of the original volume, and then is diluted with water, and acidified to pH 4 by treatment with concentrated hydrochloric acid, and extracted with ethyl acetate. The extract is 25 dried over magnesium sulphate and concentrated, to give 6-cyclopentyl-5-methoxypyridine-2-carboxylic acid (1.38 g) in the form of a yellow solid, m.p. 96-99°C.

By proceeding in a similar manner using 3-hydroxytetrahydrofuran instead of cyclopentanol as the starting material, there is prepared 5-methoxy-30 6-(tetrahydro-3-furyloxy)pyridine-2-carboxylic acid.

REFERENCE EXAMPLE 51

By proceeding in a similar manner to Reference Example 115, but replacing 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid by 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoic acid (prepared as in Reference Example 52), 35 there was prepared 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoyl chloride as an oil that was used directly in Example 1.

REFERENCE EXAMPLE 52

By proceeding in a similar manner to Reference Example 116, but replacing 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde by 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzaldehyde, there was prepared 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzoic acid as a colorless solid; m.p. 155-157°C.

- 5 ^1H NMR (CDCl_3) δ : 1.82-1.91 (m, 2H), 2.02-2.09 (m, 2H), 3.58 (ddd, 2H, $J=11$, 8, 3 Hz), 3.94 (s, 3H), 4.04 (dt, 2H, $J=11$, 4 Hz), 4.49-4.55 (m, 1H), 6.95 (d, 1H, $J=8$ Hz), 7.64 (d, 1H, $J=2$ Hz), 7.79 (dd, 1H, $J=8$, 2 Hz).

REFERENCE EXAMPLE 53

- By proceeding in a similar manner to Reference Example 117, but
10 replacing 3-hydroxytetrahydrofuran with 4-hydroxytetrahydropyran, there was prepared 4-methoxy-3-(tetrahydro-4-pyranyloxy)benzaldehyde as a colorless oil. ^1H NMR (CDCl_3) δ : 1.82-1.90 (m, 2H), 2.02-2.09 (m, 2H), 3.57 (ddd, 2H, $J=12$, 8, 2 Hz), 3.95 (s, 2H), 4.03 (dt, 2H, $J=12$, 4 Hz), 4.52-4.59 (m, 1H), 7.01 (d, 1H, $J=8$ Hz), 7.45 (d, 1H, $J=2$ Hz), 7.49 (dd, 1H, $J=8.2$ Hz), 9.85 (s, 1H).

15 REFERENCE EXAMPLE 54

- Lithium iodide (9.2 g) is added to a stirred solution of 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid (3.28 g) and heated at 160°C for 6 hours. The solid is dissolved in 2N NaOH solution (250 mL) and washed with ethyl acetate. The aqueous solution is acidified to pH 1 with concentrated HCl and
20 extracted with ethyl acetate (2 x 150 mL). The combined extracts were washed with brine, dried over MgSO_4 , evaporated under reduced pressure and triturated with ether to give 4-hydroxy-3-(tetrahydro-3-furyloxy)benzoic acid (2.31 g) as yellow solid; m.p. 210-212°C. NMR (DMSO): 12.54 (bs, 1H), 9.8 (s, 1H), 7.45 (dd, 1H, $J=8$ Hz, 2 Hz), 7.38 (d, 1H, $J=2$ Hz), 6.88 (d, 1H, $J=8$ Hz), 5.03
25 (m, 1H), 3.90-3.82 (m, 3H), 3.75 (dt, $J=8$ Hz, 4 Hz), 2.16 (m, 1H), 2.01 (m, 1H).

REFERENCE EXAMPLE 55

- Concentrated H_2SO_4 (0.3 mL) is added to a suspension of 4-hydroxy-3-(tetrahydro-3-furyloxy)benzoic acid (2.31 g) in methanol (30 mL) and heated under reflux for 7 hours. The reaction solution is evaporated under reduced
30 pressure, the residue triturated with water and extracted with ethyl acetate. The extract is dried (MgSO_4) and evaporated under reduced pressure to give a fawn solid. Purification by mpc eluting with ether gives methyl 4-hydroxy-3-(tetrahydro-3-furyloxy)benzoate as white solid. (1.92 g); m.p. 136-138°C. NMR (CDCl_3): 7.65 (dd, 1H, $J=8$ Hz, 2 Hz), 7.5 (d, 1H, $J=2$ Hz), 6.95 (d, 1H, $J=8$ Hz),
35 6.43 (bs, 1H), 5.07 (m, 1H), 4.09-3.9 (m, 4H), 3.89 (s, 3H), 2.3 (m, 1H), 2.18 (m, 1H).

REFERENCE EXAMPLE 56

Chlorodifluoromethane is bubbled slowly through a stirred mixture of methyl 4-hydroxy-3-(tetrahydro-3-furyloxy)benzoate (1.92 g), anhydrous potassium carbonate (1.56 g), and potassium iodide (0.42 g) in dimethylformamide (28 mL) at 70-75°C for 6 hours. Water (150 mL) is added and extracted with ether (2 x 100 mL). The combined extracts are washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give a pale yellow oil, which is purified by mpc, eluting with 1:1 v/v ether-pentane to give methyl 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate (1.23 g) as a colorless oil. NMR (CDCl₃): 7.67 (dd, 1H, J=8 Hz, 2 Hz), 7.58 (d, 1H, J=2 Hz), 7.22 (d, 1H, J=2 Hz), 6.62 (t, 1H, J=74 Hz), 5.05 (m, 1H), 4.05-3.90 (m, 4H), 3.92 (s, 3H), 2.32-2.15 (m, 2H).

REFERENCE EXAMPLE 57

A solution of potassium carbonate (0.72 g) in water (7 mL) is added to a solution of methyl 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate (1.23 g) in methanol (19 mL) and the solution stirred at 60-70°C for 5 hours. Methanol is removed evaporated under reduced pressure, the residue diluted with water, acidified with glacial-acetic acid and extracted with ethyl acetate. The extract is washed with brine, dried (MgSO₄) and evaporated off under reduced pressure to give 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoic acid as a white solid (1.18 g); m.p. 100-102°C. NMR (CDCl₃): 7.75 (dd, 1H, J=8 Hz, 2 Hz), 7.64 (d, 1H, J=2 Hz), 7.25 (d, 1H, J=9 Hz), 6.64 (t, 1H, J=74 Hz), 5.05 (m, 1H), 4.1-3.94 (m, 4H), 2.34-2.17 (m, 2H).

REFERENCE EXAMPLE 58

A suspension of 2-methoxyphenyl benzoate (212.5 g) in glacial acetic acid (1 L) is treated dropwise during 1 hour with a solution of bromine (51.5 mL) in glacial acetic acid (150 mL). The mixture is stirred for a further 1 hour, then it is concentrated and the residue is dissolved in t-butyl methyl ether (1500 mL). The solution is washed with water (500 mL) and with saturated aqueous sodium bicarbonate solution. The solution is then dried, filtered and concentrated, to give 2-benzoyloxy-4-bromoanisole (205.8 g), in the form of a white solid, m.p. 73-75°C.

REFERENCE EXAMPLE 59

A solution of 2-benzoyloxy-4-bromoanisole (5 g) and sodium hydroxide (3 g) in water (5 mL) and ethanol (50 mL) is heated at reflux for 1 hour 30 minutes. It is then evaporated and the residue is triturated with water (20 mL) and concentrated hydrochloric acid (10 mL) and extracted with dichloromethane (150 mL). The organic solution is washed with saturated

aqueous sodium bicarbonate solution (3 x 25 mL), dried, and concentrated, to give 5-bromo-2-methoxyphenol (3.25 g), in the form of a white crystalline solid, m.p. 67-68°C.

REFERENCE EXAMPLE 60

- 5 A stirred solution of 5-bromo-2-methoxyphenol (74 g) and anhydrous potassium carbonate (73.6 g) in dry dimethylformamide (500 mL) is treated with cyclopentyl bromide (80.5 g) and the solution is heated at 60°C for 16 hours. It is then concentrated, and the resulting residue is triturated with water (250 mL), and extracted with dichloromethane (3 x 250 mL). The combined
10 extracts are dried and evaporated, to give 3-cyclopentyloxy-4-methoxyphenyl bromide (95.5 g), in the form of a light brown oil.

REFERENCE EXAMPLE 61

- A solution of butyl lithium in hexane (5.1 mL; 2.5 M) is treated with a solution of 3-cyclopentyloxy-4-methoxyphenyl bromide (3.45 g) in dry
15 tetrahydrofuran (30 mL) at -70°C and the solution is then stirred at -70°C for 1 hour. It is then treated dropwise with 2,6-dichlorophenylacetaldehyde (2.4 g), while keeping the temperature below -60°C. When the addition is complete the temperature is allowed to rise to room temperature and the solution is stirred for a further 2 hours. The reaction mixture is treated with aqueous
20 ammonium chloride solution (50 mL) and the solution is extracted with diethyl ether (2 x 200 mL). The combined extracts are dried and concentrated, to give a yellow oil, which is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:8 v/v), to give 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)ethanol (1.6 g), in the form of a white
25 solid, m.p. 87-89°C.

 By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl bromide (that is prepared as in Reference Example 117) instead of 3-cyclopentyloxy-4-methoxyphenyl bromide, there is prepared 2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanol.

REFERENCE EXAMPLE 62

- A solution of diisopropylamine (10.5 mL) in dry tetrahydrofuran (150 mL) is cooled to -75°C and treated with a solution of butyl lithium in hexane (30 mL; 2.5 M) during 10 minutes. After stirring for 1 hour at -75°C the mixture is treated with a solution of 3,5-dichloropyridine (10.8 g) in dry tetrahydrofuran (55 mL)
35 and stirred for a further 30 minutes. It is then treated with methyl iodide (4.7 mL) in dry tetrahydrofuran (10 mL) during 10 minutes, and the solution is allowed to rise gradually to room temperature. After stirring for 2 hours, the

mixture is treated with saturated aqueous sodium bicarbonate solution (50 mL), followed by diethyl ether (100 mL). The organic layer is washed with brine, dried and evaporated, and the resulting residue is subjected to flash chromatography, to give 3,5-dichloro-4-methylpyridine (10.6 g), m.p. 46-47°C.

5 REFERENCE EXAMPLE 63

A stirred solution of diisopropylamine (9.75 mL) in dry tetrahydrofuran (200 mL) at -70°C is treated dropwise with a solution of butyl lithium in hexane (27.2 mL; 2.5 M) and the solution is stirred for 30 minutes. It is then treated with a solution of 3,5-dichloro-4-methylpyridine (10.25 g) in dry tetrahydrofuran (60 mL) during 30 minutes, while keeping the temperature below -75°C, and the solution is then stirred for a further 30 minutes. It is then treated with 3-cyclopentyloxy-4-methoxybenzaldehyde (13.92 g) in dry tetrahydrofuran (60 mL) during 15 minutes, and stirred for a further 1 hour 30 minutes at -75°C. The solution is treated with aqueous ammonium chloride solution and extracted with ethyl acetate (3 x 100 mL). The organic layers are combined, washed with brine, dried and concentrated to low volume. The resulting precipitate is filtered off, to give 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol (20.5 g), m.p. 124-125°C.

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde (that is prepared as in Reference Example 117) instead of 3-cyclopentyloxy-4-methoxybenzaldehyde, there is prepared 2-(3,5-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanol.

20 REFERENCE EXAMPLE 64

Oxalyl chloride (2 mL) is added to a stirred solution of 3-cyclopentyloxy-4-methoxybenzoic acid (2.36 g) in dry dichloromethane (50 mL) under a nitrogen atmosphere, and the mixture stirred for 3 hours. The reaction mixture is concentrated in vacuo and the residue dissolved in fresh dry dichloromethane (50 mL). N,O-dimethylhydroxylamine hydrochloride (1.12 g) and 2,4,6-collidine (2.9 mL) are added and the mixture stirred for 4 hours. The mixture is diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate (2 x 30 mL), 2 M aqueous hydrochloric acid (2 x 30 mL) and water (20 mL). The dried (MgSO₄) solution is concentrated to an orange oil (3 g) which is purified by flash chromatography (gradient elution ethyl acetate/pentane (2:3 v/v) to ethyl acetate/pentane (2:1 v/v) on silica gel column) to give 3-cyclopentyloxy-4,N-dimethoxy-N-methylbenzamide (2.5 g) as a yellow syrup.

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid (that is prepared as in Reference Example 116) instead of 3-cyclopentyloxy-4-methoxybenzoic acid, there is prepared 4,N-dimethoxy-N-methyl-3-(tetrahydro-3-furyloxy)benzamide.

5 REFERENCE EXAMPLE 65

Hydroxylamine hydrochloride (3.82 g) is added to a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (11.0 g) in acetic anhydride (30 mL) and the suspension heated in an oil bath at 100°C until refluxing starts. The heating is then removed while the exothermic reaction refluxes gently. Heating at 100°C is then continued for a further 1 hour. The dark solution is concentrated and the crude product dissolved in cyclohexane (200 mL). The solution is washed with 5% sodium bicarbonate solution (2 x 50 mL), water (2 x 50 mL) and brine (50 mL), and dried over magnesium sulfate. Upon evaporation, an amber oil (11.8 g) that is purified by flash chromatography (dichloromethane as eluant on silica gel column) gives 3-cyclopentyloxy-4-methoxybenzonitrile (8.6 g) as a pale yellow oil. [Elemental analysis: C,71.7; H,6.93; N,6.47%; calculated for C₁₃H₁₅NO₂: C,71.87; H,6.96; N,6.45%.]

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde (that is prepared as in Reference Example 117) instead of 3-cyclopentyloxy-4-methoxybenzaldehyde, there is prepared 4-methoxy-3-(tetrahydro-3-furyloxy)benzonitrile.

REFERENCE EXAMPLE 66

A stirred solution of 5-amino-2-methoxyphenol (10 g) in dry dioxane (150 mL) is treated portionwise with an oil suspension of sodium hydride (60%; 3 g; 75 mmol) and the mixture is then warmed at 60°C for 30 minutes. It is then treated dropwise with a solution of cyclopentyl bromide (9.2 mL) and potassium iodide (50 mg) in dry dimethylformamide (20 mL) and heated at reflux for 5 hours. The mixture is then concentrated and the residue is treated with ethyl acetate (200 mL) and water (200 mL). The organic layer is then separated, washed with water (100 mL), aqueous sodium hydroxide solution (250 mL; 1 N), and with water (100 mL), and dried over magnesium sulfate. The concentration of the reaction mixture gives a dark oil, which is subjected to flash chromatography, eluting with a mixture of n-hexane and ethyl acetate (1:1 v/v), to give 3-cyclopentyloxy-4-methoxyaniline (4.43 g), in the form of an oil.

35 REFERENCE EXAMPLE 67

A stirred solution of diisopropylamine (14 mL) in dry tetrahydrofuran

(150 mL), is treated dropwise with a solution of butyl lithium in hexanes (40 mL; 2.5 M), under nitrogen, while keeping the temperature at below -70°C. The resulting mixture is then stirred for a further period of 30 minutes at below -70°C. The stirred mixture, while it is still maintained at below -70°C, is then
5 treated dropwise with a solution of 4-picoline (9.3 g) in dry tetrahydrofuran (20 mL). The stirred mixture is maintained at below -70°C for a further 45 minutes. The stirred mixture, while it is still maintained at below -70°C, is then treated with a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (22.0 g) in dry tetrahydrofuran (100 mL), and it is stirred at below -70°C for a further 30
10 minutes. The resulting mixture is then allowed to warm to room temperature overnight, and then treated with saturated aqueous ammonium chloride solution (200 mL). The layers are separated and the aqueous layer is further extracted with ethyl acetate (3 x 300 mL). The combined organic extracts are dried over magnesium sulfate and evaporated to dryness. The resulting
15 residue is recrystallized from ethyl acetate, to give (\pm)-1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(pyrid-4-yl)ethanol (28.5 g), in the form of a cream solid, m.p. 102-103°C.

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde (that is prepared as in Reference Example 117) instead
20 of 3-cyclopentyloxy-4-methoxybenzaldehyde, there is prepared (\pm)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(pyrid-4-yl)ethanol.

REFERENCE EXAMPLE 68

A stirred solution of concentrated hydrochloric acid (1.7 mL) in water (5 mL) from 0°C and 5°C is treated with 3-cyclopentyloxy-4-methoxyaniline (0.83
25 g), followed by a solution of sodium nitrite (0.29 g) in water (0.6 mL), at such a rate that the temperature remains from 0°C and 5°C. The resulting solution is stirred for a further 10 minutes, while keeping the temperature below 5°C. The stirred solution, while still maintained at below 5°C, is then treated dropwise with a solution of sodium tetrafluoroborate (0.88 g) in water (1.8 mL). The
30 resulting precipitate is filtered off, washed with cold water (3 mL) and dried in vacuo, to give 3-cyclopentyloxy-4-methoxyphenyldiazonium tetrafluoroborate (1.24 g) in the form of a gray solid, m.p. 120°C.

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)aniline prepared by hydrolyzing N-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)acetamide (that is prepared as in Reference Example 117)
35 folinstead of 3-cyclopentyloxy-4-methoxyaniline, there is prepared 4-methoxy-3-(tetrahydro-3-furyloxy)phenyldiazonium tetrafluoroborate.

REFERENCE EXAMPLE 69

A stirred solution of 2-methoxyphenyl benzoate (10 g) in dichloromethane (100 mL) from 0-5°C is treated dropwise with chlorosulfonic acid (2.9 mL) and the solution is then stirred for 3 hours from 0-5°C. The precipitate which forms is filtered off, washed with cold dichloromethane, and dried in vacuo, to give 3-benzoyloxy-4-methoxybenzenesulfonic acid (11.45 g), in the form of a white solid, m.p. 139-140°C.

REFERENCE EXAMPLE 70

A solution of 3-benzoyloxy-4-methoxybenzenesulfonic acid (7.69 g) in dry toluene (70 mL) is treated with thionyl chloride (9 mL), and the mixture is heated at reflux for 6 hours. Concentration gives 3-benzoyloxy-4-methoxybenzenesulfonyl chloride (8.4 g), in the form of a brown oil.

REFERENCE EXAMPLE 71

A stirred solution of 2-chloroaniline (3.3 g) and triethylamine (3.6 mL) in dichloromethane (50 mL) is treated, portionwise, with a solution of 3-benzoyloxy-4-methoxybenzenesulfonyl chloride (8.4 g) in dichloromethane (50 mL). The reaction mixture is stirred for 6 hours at room temperature, and then it is washed with water. The organic solution is dried and concentrated in vacuo, to give an oil, which is subjected to flash chromatography on silica gel, eluting with diethyl ether, to give a mixture of N-(3-benzoyloxy-4-methoxyphenylsulfonyl)-2-chloroaniline and N,N-bis(3-benzoyloxy-4-methoxyphenylsulfonyl)-2-chloroaniline.

REFERENCE EXAMPLE 72

A solution of potassium hydroxide (1.27 g) in water (5 mL) and methanol (10 mL) is treated with a mixture of N-(3-benzoyloxy-4-methoxyphenylsulfonyl)-2-chloroaniline and N,N-bis(3-benzoyloxy-4-methoxyphenylsulfonyl)-2-chloroaniline (2.39 g; that is prepared as described in Reference Example 71) and heated at reflux for 7 hours. After cooling, the solution is neutralized by treatment with dilute hydrochloric acid (1 N), and the mixture is extracted with dichloromethane (2 x 75 mL). The combined organic extracts are dried and concentrated, to give a waxy solid. This solid is subjected to flash chromatography on silica gel, eluting with diethyl ether, to give a mixture of N-(3-hydroxy-4-methoxyphenylsulfonyl)-2-chloroaniline and N,N-bis(3-hydroxy-4-methoxyphenylsulfonyl)-2-chloroaniline (0.7 g), which is used directly in Example 49.

REFERENCE EXAMPLE 73

Vigorously stirred aqueous ammonia solution (70 mL; 32% w/w) is treated dropwise with warm molten 3-cyclopentyloxy-4-methoxybenzoyl chloride (25.7 g) during a period of 20 minutes, keeping the temperature below 20°C. Stirring is continued at 20°C for 2 hours, and then the suspension is filtered. The resulting solid is washed with water until free of ammonia, and is then dried under vacuum at 40-45°C, to give 3-cyclopentyloxy-4-methoxybenzamide (21.78 g), in the form of a buff solid.

5 By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl (that is prepared as in Reference Example 115) instead of 3-cyclopentyloxy-4-methoxybenzoyl chloride, there is prepared 4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.

REFERENCE EXAMPLE 74

A solution of 4-amino-2,3,5-trifluoropyridine [23.1 g; that is prepared as described in J.Med.Chem.30, 340-347,(1987)] and hydrazine hydrate (113 mL) in ethanol (925 mL) is stirred and heated at 100°C for 2 days. The solution is then evaporated to low volume and the resulting 4-amino-3,5-difluoro-2-hydrazinopyridine (22.5 g) is filtered off in the form of a cream solid.

This damp solid is added portionwise to a stirred solution of cupric sulfate (132 g) in water (462 mL) below 25°C, and the reaction mixture is stirred at room temperature for 48 hours. The reaction mixture is basified by treatment with aqueous potassium hydroxide solution (2 N) and extracted with dichloromethane (1500 mL). The organic layer is filtered through diatomaceous earth, dried over magnesium sulphate, and concentrated to give an off-white solid (13.72 g). This solid is subjected to mpic, using diethyl ether as eluent, to give 4-amino-3,5-difluoropyridine (3.4 g), m.p. 99-101°C. [NMR (CDCl₃): 4.32(bs,2H),8.1(s,2H)].

REFERENCE EXAMPLE 75

By proceeding in a manner similar to that described in Reference Example 3, but using the appropriate quantities of the corresponding carboxylic acids, there are prepared:

3 0 3-cyclopentylmethoxy-4-methoxybenzoyl chloride, in the form of a light brown oil;

3-cyclopropylmethoxy-4-methoxybenzoyl chloride, in the form of a light brown oil;

3 5 3-isopropoxy-4-methoxybenzoyl chloride, in the form of a golden oil;

3-tert-butoxy-4-methoxybenzoyl chloride in the form of a light brown oil; and

4-methoxy-3-(pent-3-yloxy)benzoyl chloride, in the form of a golden oil.

REFERENCE EXAMPLE 76

By proceeding in a manner similar to that described in Reference Example 6, but using the appropriate quantities of the corresponding aldehydes, there are prepared:

- 5 3-cyclopentylmethoxy-4-methoxybenzoic acid, in the form of a white solid, m.p. 148-152°C;
3-cyclopropylmethoxy-4-methoxybenzoic acid, in the form of a white solid, m.p. 158-162°C;
3-isopropoxy-4-methoxybenzoic acid, in the form of a white solid, m.p. 133-
10 135°C; and
4-methoxy-3-(pent-3-yloxy)benzoic acid, in the form of a white solid, m.p. 137-139°C. [Elemental analysis: C,65.9; H,7.7%; calculated: C,65.5; H,7.6%].

REFERENCE EXAMPLE 77

- A solution of methyl 3-tert-butoxy-4-methoxy benzoate (4.93 g) in
1.5 methanol (100 mL) is treated with a solution of potassium carbonate (3.5 g) in water (40 mL), and the solution is stirred for 4 hours at reflux. The solution is evaporated to low volume, the residue is dissolved in water (150 mL), washed with diethyl ether (100 mL) and brought to pH 4 by treatment with glacial acetic acid. The resulting mixture is extracted with ethyl acetate (2 x 100 mL). The
2.0 combined organic extracts are washed with water (50 mL), dried over magnesium sulfate, and concentrated to give 3-tert-butoxy-4-methoxybenzoic acid (1.1 g) in the form of a white solid, m.p. 177-178°C. [NMR (CDCl₃):- 7.88(dd,1H),7.76(d,1H), 6.94(d,1H),3.89(s,3H),1.39(s,9H)].

REFERENCE EXAMPLE 78

- 2.5 A stirred solution of 3-hydroxy-4-methoxybenzaldehyde (5.74 g) in dry dimethylformamide (50 mL) is treated with cyclopentylmethyl bromide (7.34 g) and potassium carbonate (15 g), and the solution is heated at 60°C for 24 hours. After cooling and filtration, the solution is evaporated to low bulk and dissolved in ethyl acetate (100 mL). The organic solution is washed with
3.0 aqueous sodium hydroxide solution (4 x 50 mL; 2 N) and water (2 x 50 mL), dried over magnesium sulfate, and evaporated to give 3-cyclopentylmethyl-4-methoxybenzaldehyde (6.5 g) in the form of a light brown oil.

- By proceeding in a similar manner, but using the appropriate quantity of isopropyl bromide, there is prepared 3-isopropoxy-4-methoxybenzaldehyde, in
3.5 the form of a light golden oil. [NMR (CDCl₃): 9.85(s,1H), 7.46(dd,1H), 7.43(d,1H), 6.98(d,1H), 4.65(m,1H), 3.94(s,3H), 1.41(d,6H)].

REFERENCE EXAMPLE 79

By proceeding in a manner similar to that described in Reference Example 1, but using the appropriate quantity of cyclopropylmethyl bromide, there is prepared 3-cyclopropylmethoxy-4-methoxy-benzaldehyde, m.p. 55-58°C. [Elemental analysis: C,70.0; H,6.85%; calculated: C,69.9; H,6.8%].

5 By proceeding in a similar manner, but using the appropriate quantity of 3-bromopentane, there is prepared 4-methoxy-3-(pent-3-yloxy)benzaldehyde, in the form of a golden oil.

REFERENCE EXAMPLE 80

10 A stirred solution of isobutylene (33 mL) in dichloromethane (60 mL) at -70°C is treated dropwise with a cooled solution of methyl 3-hydroxy-4-methoxybenzoate (6 g) in dichloromethane (60 mL), followed by trifluoromethanesulfonic acid (0.3 mL). The reaction mixture is vigorously stirred at -70°C for 3 hours and then between -70°C and -50°C overnight. It is then treated with triethylamine (0.6 mL) and allowed to warm to room
15 temperature. The resulting yellow solution is concentrated, and the residue is subjected by mpic, using diethyl ether as eluent, to give methyl 3-tert-butoxy-4-methoxybenzoate (4.93 g), m.p. 98-100°C. [Elemental analysis: C,65.7; H,7.8%; calculated: C,65.5; H,7.6%].

REFERENCE EXAMPLE 81

20 A solution of 3-[exobicyclo(2.2.1)hept-5-en-2-yloxy]-4-methoxy-benzaldehyde (8 g) and aqueous potassium hydroxide solution (1 mL; 50% w/v) in methanol (35 mL), is stirred vigorously on an oil bath at 50°C. The mixture is then treated, dropwise, with an aqueous solution of potassium hydroxide (8 mL; 50% w/v) in methanol (35 mL) with hydrogen peroxide (21
25 mL; 35% w/v), to give a slightly exothermic reaction. The solution is stirred for 2 hours at 50°C and then is evaporated to low volume. The solution is diluted with water (100 mL), adjusted to pH 5 by treatment with concentrated hydrochloric acid and filtered to give 3-[exobicyclo(2.2.1)-hept-5-en-2-yloxy]-4-methoxybenzoic acid (6.42 g), m.p. 161-163°C. [NMR (CDCl₃):
30 1.31(d,1H);1.39(d,1H);1.57(ddd,1H);1.65(d,1H);2.68(bs,1H);
2.83(bs,1H);3.67(s,3H);4.09(d,1H);5.78(dd,1H);6.06(dd,1H);6.66(d,1H);
7.30(s,1H);7.42(d,1H)].

By proceeding in a similar manner using aldehydes prepared as described in Reference Example 117, the following acids are prepared:
35 4-methoxy-3-(3,4-dihydro-2H-pyran-2-methoxy)benzoic acid;
4-methoxy-3-(3,4-dihydro-2H-pyran-6-methoxy)benzoic acid;
4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzoic acid;

4-methoxy-3-(7-oxabicyclo-[2.2.1]hept-5-en-2-oxy)benzoic acid;
4-methoxy-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)benzoic acid; and
4-methoxy-3-(2-(prop-2-yn-1-oxy)ethoxy)benzoic acid.

5 REFERENCE EXAMPLE 82

Thionyl chloride (4 mL) is added to a solution of 3-cyclopentyloxy-4-trifluoromethoxybenzoic acid (0.5 g) in dry toluene (10 mL) and the mixture is heated at 80°C for 2 hours. Toluene is evaporated off under reduced pressure, to give 3-cyclopentyloxy-4-trifluoromethoxybenzoyl chloride (0.54 g), in the
10 form of a yellow oil, which was used without further purification.

REFERENCE EXAMPLE 83

Potassium carbonate (0.43 g) and water (2 mL) are added to a solution of methyl 3-cyclopentyloxy-4-trifluoromethoxybenzoate (0.78 g) in methanol (10 mL) and the mixture is heated under reflux for 2 hours. Methanol is
15 evaporated off under reduced pressure, and the crude material is partitioned between water (75 mL) and ethyl acetate (75 mL). The organic layer is separated, and the aqueous layer is acidified with hydrochloric acid (2 N) and extracted with ethyl acetate (2 x 75 mL). The combined organic extracts are dried over magnesium sulfate and evaporated under reduced pressure, to give
20 3-cyclopentyloxy-4-trifluoromethoxybenzoic acid (0.53 g), in the form of a white solid, m.p. 116-118°C. [NMR (CDCl₃): 7.72(d,1H,J=2Hz); 7.7(dd,1H,J=8Hz, 2Hz); 7.3(d,1H,J=8Hz);4.9(m,1H,);2.0-1.6(m,8H)].

By proceeding in a similar manner using 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl (that is prepared as in Reference Example 115) instead of 3-cyclopentyloxy-4-methoxybenzoyl chloride, there is prepared 4-methoxy-3-(tetrahydro-3-furyloxy)benzamide.
25

REFERENCE EXAMPLE 84

Diisopropyl azodicarboxylate (0.61 mL) is added to a solution of methyl 3-hydroxy-4-trifluoromethoxybenzoate (0.74 g), cyclopentanol (0.19 g) and triphenylphosphine (0.81 g) in tetrahydrofuran (10 mL) and the mixture is heated overnight at reflux. Solvent is evaporated off under reduced pressure and the resulting yellow oil is triturated with diethyl ether. The white solid thus formed is filtered off, and the filtrate is evaporated under reduced pressure and subjected to mplc, to give methyl 3-cyclopentyloxy-4-trifluoromethoxybenzoate
30 in the form of a pale yellow oil (0.6 g).
35

REFERENCE EXAMPLE 85

Methyl 3-amino-4-trifluoromethoxybenzoate (2.3 g) is dissolved in a mixture of concentrated hydrochloric acid (5 mL) and water (10 mL), with slight warming. The solution is then cooled to -5°C and a solution of sodium nitrite (0.8 g) in water (2 mL) is added dropwise at that temperature and the resulting yellow solution is stirred at 0°C for 30 minutes. A small amount of undissolved solid material is filtered off, and a solution of sodium tetrafluoroborate (1.52 g) in water (2 mL) is added and the mixture is stirred at 0°C for another 30 minutes. The white solid thus formed is filtered off, washed with water and diethyl ether, and dried over phosphorus pentoxide under vacuum (yield = 2.25 g). A portion (0.5 g) of this solid is then added to a solution of cupric nitrate (150 g) in water (100 mL). The mixture is extracted with dichloromethane (2 x 100 mL), and the extracts are dried over magnesium sulfate and evaporated under reduced pressure, to give a pale yellow solid (1.4 g), which is subjected to mpc, eluting with a mixture of diethyl ether and pentane (1:4 v/v), to give methyl 3-hydroxy-4-trifluoromethoxybenzoate (1.0 g), in the form of a white solid, m.p. 95-97°C.

REFERENCE EXAMPLE 86

A solution of potassium carbonate (7.4 g) in water (72 mL) is added, dropwise, to a stirred solution of methyl 3-(tetrahydrothiophen-3-oxy)-4-methoxybenzoate (11.8 g) in methanol (200 mL) at room temperature. After the addition is complete, the solution is stirred and heated at 60-70°C for 5 hours and allowed to stand at room temperature overnight. The solution is evaporated, the residue is dissolved in water, acidified with glacial acetic acid and the precipitate formed is collected and dried, to give 3-(tetrahydrothiophen-3-oxy)-4-methoxybenzoic acid (7.4 g). m.p. 177-179°C. [Elemental analysis: C,55.3; H,5.5; calculated: C,56.7; H,5.55%].

REFERENCE EXAMPLE 87

By proceeding as described in Reference Example 7, but using the appropriate quantities of 3-hydroxythiophane and isovanillic acid methyl ester, there was prepared methyl 3-(tetrahydrothiophen-3-oxy)-4-methoxybenzoate, in the form of a golden oil. [Elemental analysis: C,55.2; H,6.8; S,8.1%; calculated: C,58.2; H,6.0; S,11.95%].

REFERENCE EXAMPLE 88

A solution of methyl 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoate (1.39 g) in methanol (22 mL) is treated with a solution of potassium carbonate (0.83 g) in water (8 mL) and the solution is heated at 60-70°C for 8 hours, cooled and evaporated. The residue is dissolved in water

- (30 mL), extracted with diethyl ether (50 mL) and acidified to pH 4 by treatment with glacial acetic acid. The precipitated solid is extracted with ethyl acetate (2 x 75 mL). The combined organic extracts are dried over magnesium sulfate and concentrated, to give 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoic acid, in the form of a white solid, m.p. 163-165°C.

REFERENCE EXAMPLE 89

- A stirred solution of methyl 3-hydroxy-4-methoxybenzoate (1.72 g), potassium iodide (0.1 g), and potassium carbonate (1.55 g) in dimethylformamide (50 mL) is treated with 1-chloromethyl-2,2,3,3-tetrafluorocyclobutane (2.0 g), and the solution is stirred at 70-80°C for 6 hours. After cooling, the reaction mixture is diluted with water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The organic extracts are combined, dried over magnesium sulfate and concentrated, to give a golden oil. The oil is subjected to flash chromatography, using diethyl ether as eluent, to give methyl 3-(4,4-difluoro-3-methylenecyclobut-1-enyloxy)-4-methoxybenzoate, m.p. 60-62°C. [Elemental analysis: C,59.5; H,4.3%; calculated: C,52.2; H,4.4%].

REFERENCE EXAMPLE 90

- By proceeding in a similar manner to Reference Example 6, but using 3-(2-fluorocyclopentyloxy)-4-methoxybenzaldehyde as the starting material, there is prepared 3-(2-fluorocyclopentyloxy)-4-methoxybenzoic acid. Mass spectrum m/z 254(M⁺).

REFERENCE EXAMPLE 91

- By proceeding in a similar manner to Reference Example 7, but using 2-trans-fluorocyclopentanol as the starting material, there is prepared 3-(2-fluorocyclopentyloxy)-4-methoxybenzaldehyde. Mass spectrum m/z 238(M⁺).

REFERENCE EXAMPLE 92

- By proceeding in a manner similar to that described in Reference Example 20, but using as the starting material the appropriate quantity of 3-isopropoxy-4-(methylthio)benzoic acid, there is prepared 3-isopropoxy-4-(methylthio)benzoyl chloride, in the form of a yellow oil.

REFERENCE EXAMPLE 93

- By proceeding in a manner similar to that described in Reference Example 19, but using as the starting material the appropriate quantity of methyl 3-isopropoxy-4-(methylthio)benzoate, there is prepared 3-isopropoxy-4-(methylthio)benzoic acid, in the form of a white solid, m.p. 127-129°C. [Elemental analysis: C,58.5; H,6.3; S,14.5%; calculated: C,58.4; H,6.2; S,14.2%].

REFERENCE EXAMPLE 94

A solution of methyl 3-isopropoxy-4-nitrobenzoate (5.7 g) in N,N'-dimethylimidazolidinone (35 mL) is treated with sodium thiomethoxide (2 g), and the mixture is stirred at room temperature for 4 hours. The mixture is then
5 diluted with water (250 mL) containing sodium chloride (47 g), and is extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are washed with brine (100 mL), dried over magnesium sulfate and evaporated in vacuo, to give a brown oil. The oil is subjected to flash chromatography, eluting with a 1.9 v/v mixture of diethyl ether and pentane, to give methyl 3-isopropoxy-4-
10 (methylthio)benzoate (4.0 g), in the form of a cream solid, m.p. 41-43°C.

REFERENCE EXAMPLE 95

A solution of methyl 3-hydroxy-4-nitrobenzoate (5.9 g) in dimethylformamide (40 mL) is treated with potassium carbonate (6.2 g) and 2-bromopropane (3.7 g), and the stirred solution is heated at 60-65°C for 4 hours.
15 After cooling, water (100 mL) is added and the solution is extracted with toluene (2 x 100 mL). The combined organic extracts are dried over magnesium sulfate and evaporated in vacuo, to give methyl 3-isopropoxy-4-nitrobenzoate, in the form of a pale yellow solid (5.9 g), m.p. 46-48°C.

REFERENCE EXAMPLE 96

By proceeding in a manner similar to that described in Reference Example 63, but using as the starting material the appropriate quantity of (±)-3-[(exo)-8,9,10-trinorbornyl-2-oxy]-4-methoxybenzaldehyde 1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzaldehyde, there are prepared:
20 after flash chromatography, eluting with a mixture of ethyl acetate and pentane (1:2v/v), rac-1-[3-[(exo)-8,9,10-trinorbornyl-2-oxy]-4-methoxyphenyl]-2-(3,5-dichloropyrid-4-yl)ethanol, in the form of a yellow oil; and
25 1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]-2-(3,5-dichloropyrid-4-yl)ethanol.

REFERENCE EXAMPLE 97

By proceeding in a manner similar to that described in Reference Example 63, but using as the starting material the appropriate quantity of 3-cyclopentyloxy-4-(methylthio)benzaldehyde and 4-(methylthio)-3-(tetrahydro-3-furyloxy)benzaldehyde, there are prepared:
30 1-[3-cyclopentyloxy-4-(methylthio)phenyl]-2-(3,5-dichloropyrid-4-yl)ethanol, in the form of a white solid, m.p. 122-123°C. [Elemental analysis: C, 57.3; H, 5.3; Cl, 17.6; N, 3.4; S, 8.4%; calculated: C, 57.3; H, 5.3; Cl, 17.8; N, 3.5; S, 8.1%]; and
35

1-(3-(tetrahydro-3-furyloxy)-4-(methylthio)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanol.

REFERENCE EXAMPLE 98

A solution of 4-bromo-2-cyclopentyloxy-1-(methylthio)benzene (13.2 g) in dry tetrahydrofuran (100 mL) under nitrogen is treated at -70°C with a solution of butyllithium in hexane (20.24 mL; 2.5 M) and the resulting solution is stirred for 1 hour at this temperature. It is then treated with dimethylformamide (7.12 mL), followed by boron trifluoride diethyl etherate (11.32 mL), keeping the temperature at -65°C. When the addition is complete the reaction mixture is allowed to warm to room temperature and is then poured into ice-water (450 mL) and extracted with dichloromethane (3 x 400 mL). The combined extracts are dried over magnesium sulfate and concentrated to give an oil, which is subjected to flash chromatography, eluting with a mixture of dichloromethane and cyclohexane (3:7 v/v), to give 3-cyclopentyloxy-4-(methylthio)-benzaldehyde (6.2 g). [NMR (DMSO): 9.91(S,1H), 7.53(dd,1H), 7.36(d,1H), 7.33(d,1H), 5.01 (m,1H), 2.44(s,3H), 2.0-1.5(m,8H)].

By proceeding in a manner similar, but using 4-bromo-2-(tetrahydro-3-furyloxy)-1-(methylthio)benzene (that is prepared as described in Reference Example 117) as the starting material, there is prepared 4-(methylthio)-3-(tetrahydro-3-furyloxy)benzaldehyde.

REFERENCE EXAMPLE 99

A stirred solution of 4-bromo-2-hydroxythioanisole (15.9 g) and cyclopentyl bromide (16.05 g) in dry dimethylformamide (170 mL) is treated with anhydrous potassium carbonate (14.7 g) and the mixture is heated at 60°C for 1 day. After cooling, the solution is diluted with water (250 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts are dried over magnesium sulfate and concentrated. The residue is subjected to flash chromatography, eluting with a mixture of ethyl acetate and pentane (5:95 v/v), to give 4-bromo-2-cyclopentyloxy-1-(methylthio)benzene, in the form of an oil (17.2 g). [NMR (DMSO): 7.14-7.03(m,3H), 4.93(m,1H), 2.33(s,3H), 2.0-1.53(m,8H)].

REFERENCE EXAMPLE 100

By proceeding in a manner similar to that described in Reference Example 63, but using as the starting materials the appropriate quantities of 4-methoxy-3-prop-2-yloxybenzaldehyde and 4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)benzaldehyde, there are prepared:

- 1-(4-methoxy-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol, in the form of a buff solid, m.p. 132-133°C. [Elemental analysis: C,57.2; H,5.37; Cl,19.8; N,3.80%; calculated: C,57.32; H,5.38; Cl,19.9; N,3.93%]; and
5. 2-(3,5-dichloropyrid-4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanol.

REFERENCE EXAMPLE 101

- A mixture of 3-hydroxy-4-methoxybenzaldehyde (20.0 g), anhydrous potassium carbonate (26.2 g) and 2-bromopropane (18.3 mL) in dry dimethylformamide (300 mL) is stirred and heated at 55-65°C for 24 hours.
- 1 0 The cooled mixture is poured into water and extracted with ethyl acetate. The extract is dried over magnesium sulfate and concentrated in vacuo at 40°C, to give 4-methoxy-3-prop-2-yloxybenzaldehyde, in the form of an oil (24.2 g).

REFERENCE EXAMPLE 102

- By proceeding in a manner similar to that described in Example 63, but
- 1 5 using as the starting material the appropriate quantity of 4-methylthio-3-prop-2-yloxybenzaldehyde, there is prepared 1-(4-methylthio-3-prop-2-yloxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol, in the form of a buff solid, m.p. 106-108°C. [Elemental analysis: C,55.1; H,5.23; N,3.73%; calculated: C,54.84; H,5.14; N,3.76%].

2 0 REFERENCE EXAMPLE 103

- A solution of n-butyllithium in hexanes (14.82 mL; 2.5 M) is added to a solution of 4-bromo-2-prop-2-yloxythioanisole (8.8 g) in dry tetrahydrofuran (70 mL), whilst cooling the mixture to -70°C under nitrogen. The mixture is stirred for 1 hour at -70°C. Dry dimethylformamide (5.22 mL) and boron trifluoride
- 2 5 diethyl etherate (8.29 mL) are added sequentially and the mixture is allowed to warm to room temperature. The mixture is poured into water and the product is extracted with dichloromethane. The extract is dried over magnesium sulfate and concentrated in vacuo, and the residue is subjected to flash chromatography on silica gel, eluting with a mixture of pentane and ethyl
- 3 0 acetate (9:1 v/v) to give 4-methylthio-3-prop-2-yloxybenzaldehyde, in the form of a soft yellow solid, m.p. 50-54°C.

REFERENCE EXAMPLE 104

- By proceeding in a manner similar to that described in Reference Example 99, but using as the starting material the appropriate quantity of 2-bromopropane, there is prepared 4-bromo-2-prop-2-yloxythioanisole, in the form of a colourless oil.
- 3 5

REFERENCE EXAMPLE 105

By proceeding in a manner similar to that described in Reference Example 63, but using as the starting materials the appropriate quantities of 3-cyclopentyloxy-4-difluoromethoxybenzaldehyde and 4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzaldehyde, there are prepared:

5. 1-(3-cyclopentyloxy-4-difluoromethoxyphenyl)-2-(3,5-dichloropyrid-4-yl)ethanol, in the form of a pale yellow solid, m.p. 121-123°C. [Elemental analysis: C,55.2; H,4.6; N,3.3; Cl,16.7%; calculated: C,54.6; H,4.6; N,3.35; Cl,16.95%]; and 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanol.

10 REFERENCE EXAMPLE 106

A solution of 3-cyclopentyloxy-4-hydroxybenzaldehyde (5.1 g) in dimethylformamide (50 mL) is treated with potassium carbonate (4.83 g) and potassium iodide (1.2 g) and the solution is heated at 70-75°C whilst difluorochloromethane is bubbled through it at a slow rate, during 5 hours.

- 15 Water (100 mL) is added and the mixture is extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are dried over magnesium sulfate and concentrated to give a brown oil. The oil is subjected to flash chromatography, eluting with a mixture of diethyl ether and pentane (1:4 v/v), to give 3-cyclopentyloxy-4-difluoromethoxybenzaldehyde, in the form of a pale
20 yellow oil (4.7 g). [NMR (CDCl₃): 9.92(s,1H); 7.5-7.24(m,3H); 6.34-5.96(t,1H); 4.9(m,1H); 2.0-1.6(m,8H)].

REFERENCE EXAMPLE 107

By proceeding in a manner similar to that described in Reference Example 63, but using as the starting materials the appropriate quantity of
25 3-[(exo)-bicyclo(2.2.1)hept-5-en-2-yloxy]-4-methoxybenzaldehyde and 4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)benzaldehyde, there are prepared:

- 2-(3,5-dichloropyrid-4-yl)-1-[3-[(exo)-bicyclo(2.2.1)hept-5-en-2-yloxy]-4-methoxyphenyl]ethanol. [NMR (CDCl₃): 1.2-1.4(m,1H); 1.45-1.6(m,1H); 1.65-
30 1.8(m,1H); 1.9(m,1H); 2.1(bs,1H); 2.9(bs,1H); 3.05(bd,J=14Hz,1H); 3.25(dd,J=5Hz,J=12Hz,1H); 3.4-3.5(m,1H); 3.84(s,3H); 4.28(bm,1H); 5.05(m,1H); 6.02(m,1H); 6.3(m,1H); 6.8-6.95(m,3H); 8.42(s,2H)];
2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanol.

35 REFERENCE EXAMPLE 108

By proceeding in a manner similar to that described in Example 63, but using as the starting materials the appropriate quantities of 4-(difluoro-

methoxy)-3-isopropoxybenzaldehyde and 4-difluoromethoxy-3-(1-methoxyprop-2-oxy)benzaldehyde, there are prepared:

- 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-isopropoxyphenyl)ethanol, in the form of a white solid, m.p. 125-126°C. [Elemental analysis: C,52.3; H,4.4; N,3.5; Cl,18.1%; calculated: C,52.1; H,4.4; N,3.6; Cl,18.1%]; and
- 5 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)-phenyl)ethanol.

REFERENCE EXAMPLE 109

- A solution of 4-hydroxymethyl-3,5-dichloropyridine (3.0 g) and N-bromosuccinimide (6.1 g) in dry dimethylformamide (100 mL) at cold 0°C is treated with triphenylphosphine (8.9 g), portionwise, during 5 minutes. The resulting red solution is stirred at 0°C for 45 minutes, and then treated with methanol (5 mL), followed by water (300 mL). The mixture is extracted with diethyl ether (4 x 200 mL), the combined organic washings dried over sodium
- 1 0
- 1 5 sulfate, and the solvent removed under reduced pressure. The resulting residue is chromatographed on silica gel, eluting with a mixture of diethyl ether and pentane (1:2 v/v), to give 4-bromomethyl-3,5-dichloropyridine (3 g), in the form of an off-white solid, m.p. 40-44°C.

REFERENCE EXAMPLE 110

- A solution of 4-formyl-3,5-dichloro-pyridine (3.0 g) in ethanol (50 mL) at 0°C is treated with sodium borohydride (0.7 g), portionwise, during 5 minutes. The resulting mixture is stirred at 0°C for 10 minutes, and then treated with aqueous hydrochloric acid (5 mL; 2 M), followed by basification to pH 7 by treatment with saturated aqueous sodium hydrogen carbonate solution. The
- 2 0
- 2 5 mixture is diluted with water (500 mL) and extracted with ethyl acetate (4 x 150 mL). The combined organic washings are dried over magnesium sulfate, and the solvent removed under reduced pressure. The resulting residue is recrystallised from t-butyl methyl ether to give 4-hydroxymethyl-3,5-dichloropyridine (2.0 g), in the form of a white solid, m.p. 87-88°C.

REFERENCE EXAMPLE 111

By proceeding in a manner similar to that described in Reference Example 62, but using instead of methyl iodide the appropriate quantity of dimethylformamide, there is prepared 4-formyl-3,5-dichloropyridine, in the form of an off-white solid, m.p. 73-75°C.

REFERENCE EXAMPLE 112

A mixture of 3,4-dimethoxy-6-fluorobenzaldehyde (3.70 g) and concentrated sulphuric acid (30 mL) is heated on a steam bath for 19 hours.

- The mixture is cooled, treated with ice-water (100 g) and stirred at 0°C for 30 minutes. The mixture is extracted with chloroform (5x100 mL). The combined organic extracts are extracted with aqueous sodium hydroxide solution (2x200 mL; 2N). These aqueous extracts are acidified, by treatment with
- 5 concentrated hydrochloric acid, with cooling, and the rust coloured solid formed is subjected to flash chromatography [using a solvent gradient of 3:1 to 2:1v/v petroleum ether (b.p.60-80°C) and ethyl acetate as eluent on a silica gel column], to give 6-fluoro-3-hydroxy-4-methoxybenzaldehyde (1.67 g) in the form of a white solid, m.p. 153-154°C. [NMR (DMSO):- 9.56(s,1H),
- 10 7.12(d,1H,J=8Hz),7.01(d,1H,J=12Hz),3.88(s,3H)].

REFERENCE EXAMPLE 113

- A mixture of 6-fluoro-3-hydroxy-4-methoxybenzaldehyde (2 g), potassium carbonate (1.66 g) and anhydrous dimethylformamide (20 mL) is treated with cyclopentyl bromide (1.62 mL) and heated on a steam bath for 43
- 15 hours. The mixture is cooled, poured into water (200 mL) and extracted with diethyl ether (3x100 mL). The combined ethereal extracts are washed with sodium hydroxide solution (2x50 mL; 2N), and brine (2x50 mL), dried over magnesium sulphate and concentrated. The residual brown oil is subjected to flash chromatography [a solvent gradient of 9:1 to 4:1v/v petroleum ether
- 20 (b.p.60-80°C) and ethyl acetate is used as eluent on a silica gel column] to give 3-cyclopentyloxy-6-fluoro-4-methoxybenzaldehyde (1.42 g) in the form of a yellow oil. [NMR (CDCl₃):-10.22(s,1H),7.27(d,1H,J=8Hz),6.63(d,1H,J=16Hz), 4.81-4.76(m,1H),3.91(s,3H),2.01-1.57(m,8H)].

REFERENCE EXAMPLE 114

- 25 A solution of 3-cyclopentyloxy-6-fluoro-4-methoxybenzaldehyde (1.40 g) in glacial acetic acid (20 mL) is treated with sulfamic acid (0.82 g) at room temperature and stirred for 10 minutes. The resulting yellow solution is cooled to 0°C and treated with a solution of sodium chlorite (0.69 g of an 80% pure sample) in water (20 mL) during 10 minutes. The resulting yellow suspension
- 30 is stirred at room temperature for 3 hours, poured into water (100 mL) and filtered to give 3-cyclopentyloxy-6-fluoro-4-methoxybenzoic acid (0.88 g), in the form of a white solid. [NMR (CDCl₃):- 7.46 (d,1H,J=8Hz),6.65(d,1H,J=12Hz), 4.80-.76(m,1H),3.90(s,3H), 2.01-1.58(m,8H)].

REFERENCE EXAMPLE 115

- 35 To a suspension of 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid (2.38 g) in dry toluene (50 mL) was added thionyl chloride (10 mL) and the mixture heated at 100°C for 2 hours. The solution was concentrated to give 2.7

g of 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride as an oil which was used directly in Example 1.

By proceeding in a similar manner using the acids of Reference Example 116, the corresponding benzoyl chlorides are prepared:

- 5 3-(2-ethoxyethoxy)-4-methoxybenzoyl chloride;
- 4-methoxy-3-(2-methoxyethoxy)benzoyl chloride;
- 3-(2-(2-butoxyethoxy)ethoxy)-4-methoxybenzoyl chloride;
- 4-methoxy-3-((exo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzoyl chloride;
- 4-methoxy-3-((endo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzoyl chloride;
- 10 4-methoxy-3-(tetrahydro-2H-pyran-2-methoxy)benzoyl chloride;
- 4-methoxy-3-(1-methoxyprop-2-oxy)benzoyl chloride;
- 4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride;
- 4-methoxy-3-(2-isopropoxyethoxy)benzoyl chloride;
- 4-methoxy-3-(3-methoxy-1-butoxy)benzoyl chloride;
- 15 4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoyl chloride;
- 4-methoxy-3-(3,4-dihydro-2H-pyran-2-methoxy)benzoyl chloride;
- 4-methoxy-3-(3,4-dihydro-2H-pyran-6-methoxy)benzoyl chloride;
- 4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzoyl chloride;
- 4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)benzoyl chloride;
- 20 6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride;
- 4-methoxy-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)benzoyl chloride; and
- 4-methoxy-3-(2-(prop-2-yn-1-oxy)ethoxy)benzoyl chloride.

REFERENCE EXAMPLE 116

- 25 A solution of 4-methoxy-3-(tetrahydrofuryloxy)benzaldehyde (9 g) in glacial acetic acid (70 mL) and sulfamic acid (7.8 g) was stirred at room temperature and then cooled in an ice bath. A solution of sodium chloride (7.2 g) in water (70 mL) was added dropwise with cooling, keeping the temperature between 13-15°C. After stirring at room temperature for 3 hours, the solution
- 30 was diluted with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were dried (MgSO₄) and concentrated to give 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid as a pale yellow solid. (7.38g). ¹H NMR (CDCl₃) δ: 2.2-2.3 (m, 2H), 3.92 (s, 3H), 3.93 (m, 1H), 4.05 (m, 3H), 5.03 (m, 1H), 6.95 (d, 1H, J = 8Hz), 7.55 (d, 1H, J = 2Hz), 7.79 (dd, 1H,
- 35 J = 8Hz, 2Hz).

By proceeding in a similar manner using the aldehydes of Reference Example 117, the corresponding acids are prepared:

- 3-(2-ethoxyethoxy)-4-methoxybenzoic acid;
 4-methoxy-3-(2-methoxyethoxy)benzoyl chloride;
 3-(2-(2-butoxyethoxy)ethoxy)-4-methoxybenzoic acid;
 4-methoxy-3-((exo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzoic acid;
 5 4-methoxy-3-((endo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzoic acid;
 4-methoxy-3-(tetrahydro-2H-pyran-2-methoxy)benzoic acid;
 4-methoxy-3-(1-methoxyprop-2-oxy)benzoic acid;
 4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid;
 4-methoxy-3-(2-isopropoxyethoxy)benzoic acid;
 10 4-methoxy-3-(3-methoxy-1-butoxy)benzoic acid;
 4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzoic acid;
 4-methoxy-3-(3,4-dihydro-2H-pyran-2-methoxy)benzoic acid;
 4-methoxy-3-(3,4-dihydro-2H-pyran-6-methoxy)benzoic acid;
 4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzoic acid;
 15 4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)benzoic acid;
 6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid;
 4-methoxy-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-xy)benzoic acid; and
 4-methoxy-3-(2-(prop-2-yn-1-oxy)ethoxy)benzoic acid.

20 REFERENCE EXAMPLE 117

- To a solution of isovanillin (9.13 g), 3-hydroxytetrahydrofuran (4.85 g) and triphenylphosphine (15.7 g) in dry tetrahydrofuran (150 mL) was added dropwise diisopropylazadicarboxylate (12.13 g) and the mixture was then stirred at reflux overnight. The solution was then concentrated and the residue
- 25 triturated with ether/pentane. After filtration, the solution was treated with ether (250 mL), washed with 3N sodium hydroxide (2 x 250 mL), water (250 mL), dried (MgSO₄) and concentrated to give a pale brown oil. The residue was purified by flash chromatography on silica gel, eluting with ether/pentane (7:3 v/v), to give 9 g of 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde as a pale
- 30 yellow oil. ¹H NMR (CDCl₃) δ: 2.15-2.35 (m, 2H), 3.9 (m, 1H), 3.95 (s, 3H), 4.05 (m, 3H), 5.03 (m, 1H), 7.0 (d, 1H, J = 8Hz), 7.35 (d, 1H, J = 2Hz), 7.48 (dd, 1H, J = 8Hz, 2Hz).

- By proceeding in a similar manner, but using isovanillin, 6-fluoro-3-hydroxy-4-methoxybenzaldehyde, 3-hydroxy-4-trifluoromethoxybenzoate or
- 35 methyl 5-hydroxy-6-methoxynicotinate and 3-hydroxytetrahydrofuran, 2-ethoxyethanol, 2-methoxyethanol, 2-(2-butoxyethoxy)ethanol, (exo)-2-oxabicyclo[2.2.1]-heptan-6-ol, (endo)-2-oxabicyclo[2.2.1]heptan-6-ol,

- tetrahydrofuryl alcohol, tetrahydro-2*H*-pyran-2-methanol, 1-methoxy-2-propanol, 2-isopropoxyethanol, 3-methoxy-1-butanol, 7-oxabicyclo[2.2.1]heptan-2-ol, 3,4-dihydro-2*H*-pyran-2-methanol, 3,4-dihydro-2*H*-pyran-6-methanol, 4-methoxy-3-methylbut-1-en-3-ol, 7-oxabicyclo-[2.2.1]hept-5-en-2-ol, 5-bromo-2-methoxyphenol, 5-acetamido-2-methoxyphenol, 4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-ol, 4-bromo-2-hydroxythioanisole and 2-(prop-2-yn-1-oxy)ethanol, there are prepared:
- 3-(2-ethoxyethoxy)-4-methoxybenzaldehyde;
 4-methoxy-3-(2-methoxyethoxy)benzaldehyde;
 10 3-(2-(2-butoxyethoxy)ethoxy)-4-methoxybenzaldehyde;
 4-methoxy-3-((exo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzaldehyde;
 4-methoxy-3-((endo)-2-oxabicyclo[2.2.1]heptan-6-oxy)benzaldehyde;
 4-methoxy-3-(tetrahydro-2*H*-pyran-2-methoxy)benzaldehyde;
 4-methoxy-3-(1-methoxyprop-2-oxy)benzaldehyde;
 15 4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde;
 4-methoxy-3-(2-isopropoxyethoxy)benzaldehyde;
 4-methoxy-3-(3-methoxy-1-butoxy)benzaldehyde;
 4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzaldehyde;
 4-methoxy-3-(3,4-dihydro-2*H*-pyran-2-methoxy)benzaldehyde;
 20 4-methoxy-3-(3,4-dihydro-2*H*-pyran-6-methoxy)benzaldehyde;
 4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzaldehyde;
 4-methoxy-3-(7-oxabicyclo-[2.2.1]hept-5-en-2-oxy)benzaldehyde;
 4-methoxy-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)benzaldehyde;
 25 4-methoxy-3-(2-(prop-2-yn-1-oxy)ethoxy)benzaldehyde;
 6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde;
 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl bromide;
 4-bromo-2-(tetrahydro-3-furyloxy)-1-(methylthio)benzene;
 N-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl) acetamide;
 30 methyl 5-(tetrahydro-3-furyloxy)-6-methoxynicotinate; and
 3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzoate

REFERENCE EXAMPLE 118

By proceeding in a similar manner to Reference Example 115, but using the appropriate quantities of the acids prepared as described in Reference Example 119, the following acid chlorides were synthesised.

- 5 (S)-(+)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride,
(R)-(-)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoyl chloride,
(±)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzoyl chloride, and
(±)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carbonyl chloride.

REFERENCE EXAMPLE 119

- 10 By proceeding in a similar manner to Reference Example 116 but using the appropriate quantities of the aldehydes prepared as described in Reference Example 120, the following acids were synthesised.

- (S)-(+)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid, m.p. 136-138°C;
specific rotation [25°C, Na D line] = (-) 11.58°,
15 (R)-(-)-4-methoxy-3-(tetrahydro-3-furyloxy)benzoic acid, m.p. 139-141°C;
specific rotation [25°C, Na D line] = (+) 10.47°,
(±)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzoic acid, and
(±)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoic acid, m.p. 76-82°C.

REFERENCE EXAMPLE 120

- 20 By proceeding in a similar manner to Reference Example 117, but using the appropriate quantities of the corresponding alcohols, the following aldehydes were synthesised.

- (S)-(+)-4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde,
(R)-(-)-4-methoxy-3-(tetrahydro-3-furyloxy)benzaldehyde,
25 (±)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzaldehyde, and
(±)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzaldehyde.

REFERENCE EXAMPLE 121

- A stirred solution of (±)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)-benzoic acid (1.09 g) in methanol (20 ml) was treated with concentrated
30 sulphuric acid (0.1 ml), and the mixture was heated at reflux for 6 hours. After cooling, the solution was concentrated, to give a golden-coloured oil. It was then subjected to mpic on silica gel, using ether as eluent, to give methyl
(±)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzoate (1.17 g). NMR
(CDCl₃) 7.67 (dd, 1 H), 7.58 (d, 1 H), 7.21 (dd, 1 H), 6.8-6.42 (t, 3 H), 5.05 (m,
35 1 H), 4.06-3.92 (m, 4 H), 3.91 (s, 3H), 2.31-2.14 (m, 2 H).

REFERENCE EXAMPLE 122

A solution of methyl (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carboxylate (4 g) in methanol (90 ml) was treated dropwise with a solution of potassium carbonate (2.67 g) in water (25 ml), and the reaction mixture was heated at reflux for 3 hours. After cooling, the solution was concentrated in vacuo. The resulting residue was dissolved in water (30 ml), and the solution was acidified to pH5 by treatment with glacial acetic acid. The solution was then concentrated in vacuo, the resulting residue was dissolved in a minimum quantity of brine, and extracted with dichloromethane (2 x 75 ml). The organic extract was dried (magnesium sulphate) and concentrated in vacuo, to give (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carboxylic acid in the form of a cream solid (0.7 g). The aqueous solution was concentrated to dryness and the resulting residue was heated at reflux for 0.5 hours in dichloromethane (75 ml). The solution was filtered, and the filtrate was concentrated, to give a further quantity of (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carboxylic acid (3.72 g). NMR (DMSO_{d6}) 8.0 (s, 1 H), 7.55 (s, 1 H), 5.11 (t, 1 H), 3.82 (s, 3 H), 3.9-3.71 (m, 4 H), 2.3-2.2 (m, 1 H), 2.0-1.92 (m, 1 H).

REFERENCE EXAMPLE 123

A suspension of triphenylphosphine (10.48 g), methyl 5-methoxy-4-pyridone-2-carboxylate (7.33 g) and (\pm)-3-hydroxytetrahydrofuran (3.26 g) in dry tetrahydrofuran (360 ml) under nitrogen was treated dropwise with diisopropyl diazodicarboxylate (8.09 g), and then it was heated at reflux for 24 hours. The mixture was filtered and concentrated in vacuo, to give a yellow oil. This oil was subjected to mpc on silica gel, eluting with a mixture of ether and dichloromethane (19:1v/v), to give methyl (\pm)-5-methoxy-4-(tetrahydro-3-furyloxy)pyridine-2-carboxylate (7.1 g), m.p. 97-99°C. NMR (CDCl₃) 8.23 (s, 1 H), 7.61 (s, 1 H), 5.1 (m, 1 H), 4.01 (s, 3 H), 4.1-3.9 (m, 4 H), 2.38-2.16 (m, 2 H).

REFERENCE EXAMPLE 124

Hydrogen chloride gas was passed into a suspension of 5-methoxy-4-pyridone-2-carboxylic acid (60.89 g) in methanol (800 mL) with ice bath cooling to 0-5°C. After 2 hours the passage of hydrogen chloride was stopped and then the mixture was refluxed gently for 5 hours. After cooling the solution was allowed to stand overnight. The precipitate was collected, and the filtrate was evaporated to dryness. The collected solid and the residue were combined, dissolved in the minimum amount of water and then brought to pH 8 by treatment with aqueous sodium bicarbonate solution. The solution was extracted with n-butanol and the extract was evaporated in vacuo, to give

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methyl 5-methoxy-4-pyridone-2-carboxylate (38.3 g), as a pale yellow solid, m.p 185-186°C.

The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are cyclic AMP phosphodiesterase inhibitors, in particular type IV cyclic AMP phosphodiesterase inhibitors. The present invention provides compounds of formula I, and compositions containing compounds of formula I, which are of use in a method for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase. For example, compounds within the present invention are useful as bronchodilators and asthma-prophylactic agents and agents for the inhibition of eosinophil accumulation and of the function of eosinophils, e.g. for the treatment of inflammatory airways disease, especially reversible airway obstruction or asthma, and for the treatment of other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. As further examples of conditions which can be ameliorated by the administration of inhibitors of cyclic AMP phosphodiesterase such as compounds of formula I there may be mentioned inflammatory diseases, such as atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatic arthritis, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome and diabetes insipidus, other proliferative skin diseases such as keratosis and various types of dermatitis, conditions associated with cerebral metabolic inhibition, such as cerebral senility, multi-infarct dementia, senile dementia (Alzheimer's disease), and memory impairment associated with Parkinson's disease, and conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke, and intermittent claudication. A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

The compounds are also inhibitors of tumor necrosis factor, especially $\text{TNF-}\alpha$. Thus, the present invention provides compounds of formula I, and compositions containing compounds of formula I, which are of use in a method for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\text{TNF-}\alpha$. For example compounds of the present invention are useful in joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis. Additionally, the compounds are useful in treatment of sepsis, septic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, asthma and other chronic pulmonary

diseases, bone resorption diseases, reperfusion injury, graft vs. host reaction and allograft rejection. Furthermore, the compounds are useful in the treatment of infections such as viral infections and parasitic infections, for example malaria such as cerebral malaria, fever and myalgias due to infection, HIV, AIDS, cachexia such as cachexia secondary to AIDS or to cancer. Other disease states that may be treated with the compounds of the present invention include Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia. A special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase or of TNF, especially TNF- α , for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting cyclic AMP phosphodiesterase and/or TNF and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, rectally or orally, but they are preferably administered by inhalation.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or

suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

- 5 The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and
10 disintegrating agents such as starch, alginic acids and certain complex silica gels combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or
15 agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

- For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame
20 oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection.
25 The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

- 30 Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

- 35 Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be
5 determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10,
10 mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence
15 the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary
20 to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

25 Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. The following pharmacological test results are typical characteristics of compounds of the present invention.

30 1. Inhibitory effects of compounds on PDE activity.

1.1 Preparation of PDE isozymes from pig aorta.

The method is described fully by Souness and Scott (*Biochem. J.*, 291, 389-395, 1993). Briefly, aortas of freshly slaughtered pigs are placed in Hepes buffered krebs solution, extraneous tissue on the outside of the aorta is
35 trimmed off and the endothelial layer on the intimal surface is removed by rubbing with a cotton swab. Smooth muscle strips are plucked from the aorta and 25 g are homogenized using a Waring Blender in homogenization buffer

(20 mM Tris/HCl, pH 7.5, 2 mM MgCl₂, 1 mM dithiothreitol, 5 mM EDTA and 1mg/ml aprotinin). The homogenate is further homogenized with an Ultra-Turrax and then centrifuged (3000 g, 5 minutes). The supernatant is removed, and the pellet is sonicated in a small volume (25-50 mL) of homogenization buffer. The sonicate is centrifuged (3000 g, 5 minutes), the pellet discarded and the supernatant is pooled with that from the first centrifugation step. The pooled supernatants are centrifuged (100,000 g, 1 hour), the resulting high-speed supernatant is filtered (0.45 µm) and then applied to a DEAE-trisacryl (IBF) column (50 x 2.44 cm) preequilibrated in column buffer (20 mM Tris/HCl, pH 7.5, 2 mM MgCl₂, 1 mM dithiothreitol, 20 µM TLCK). The column is washed with 500-700 mL of column buffer and PDE activities are eluted with 2 successive linear gradients of NaCl (0-200 mM, 400 mL and 200-300 mM, 200 mL) in column buffer. The fractions in the separated peaks of activity corresponding to the different PDE isozymes are pooled and stored at -20°C in 30% (v/v) ethylene glycol.

1.2 Measurement of PDE activity.

PDE activity is determined by the two-step radioisotopic method of Thompson et al., Adv. Cyclic Nucl. Res., 10, 69-92 (1979). The reaction mixture contains 20 mM Tris/HCl (pH 8.0), 10 mM MgCl₂, 4 mM 2-mercaptoethanol, 0.2 mM EGTA and 0.05 mg of BSA/mL. The concentration of substrate is 1 µM.

The IC₅₀ values for the compounds examined are determined from concentration-response curves in which concentrations range from 0.1 nM to 40 µM.

1.3 Results.

Compounds within the scope of the invention produce up to about 50% inhibition of porcine aortic cyclic AMP-specific phosphodiesterase (PDE IV) at concentrations from about 10⁻⁹ M up to about 10⁻⁵ M, preferably from about 10⁻⁹ up to about 10⁻⁸ M. The compounds of the invention are from about 10,000-fold to about 50-fold more selective for cyclic AMP phosphodiesterase IV than cyclic nucleotide phosphodiesterase types I, III or V.

2. Inhibitory effects of compounds on eosinophil superoxide generation.

2.1 Preparation of guinea-pig eosinophils.

The method is described fully in Souness et al (Biochem. Pharmacol. 42, 937-945, 1991).

2.2 Measurement of superoxide generation.

Superoxide anion generation is determined as the superoxide dismutase inhibitable reduction of p-iodonitrotetrazolium violet (INTV) (Souness et al, Biochem. Pharmacol. 42, 937-945, 1991). Briefly, cells are incubated in 96 well microtitre plates in 0.25 mL of Hanks buffered salt solution (HBSS) containing INTV (0.5mg/mL) plus other additions for 45 minutes at 37°C. The cells are then centrifuged at 500 g for 5 minutes and the supernatant is aspirated. The pellet is solubilized by incubation overnight at room temperature in DMSO containing 0.6 M HCl and the absorbance of the reduced dye is measured at 492 nm. The results are expressed in absorbance units.

2.3 Results.

Compounds within the scope of the invention produce up to about 50% inhibition of superoxide generation from eosinophils harvested from the peritoneal cavities of guinea-pigs at concentrations from about 10^{-8} M to about 10^{-5} M, preferably from about 10^{-8} M up to about 10^{-7} M.

3. Effects of compounds on tracheal smooth muscle contractility.

3.1 Preparation of guinea-pig tracheal strips and contractility studies.

Organ bath studies are performed essentially according to Tomkinson *et al* (Br. J. Pharmacol. 108 57-61, 1993). Briefly, tracheas are removed from male, Dunkin-Hartley guinea-pigs (400-500 g) are placed in Krebs Ringer Bicarbonate (KRB) solution and fat and connective tissue are dissected away. Epithelium is removed by mechanical abrasion and the tracheal strips are suspended under an applied load, such that they are at their optimal length, derived from preliminary experiments, and equilibrated for 90 minutes, washing at 15 minute intervals.

Cumulative concentration-response curves to spasmogens are constructed and the concentration producing 30% of maximum contraction (EC_{30}) is determined by computerized linear regression analysis. For relaxant studies, tissues are contracted with spasmogens (such as methacholine, histamine, leukotriene D₄) (EC_{30}) and when the response plateaus, PDE inhibitors (10 nM-100 μ M) or vehicle control (DMSO) are added cumulatively. The concentration of relaxant producing 50% inhibition (IC_{50}) of the agonist response is calculated by linear regression. Alternatively, PDE inhibitors, as above, may be added to tissues under basal tone and the concentration producing 50% relaxation (EC_{50}) calculated as above.

3.2 Results.

Compounds within the scope of the invention produce about 50% relaxation of guinea-pig tracheal strips (under basal tone or which had been contracted by treatment with spasmogens) at concentrations from about 5×10^{-9} M to about 10^{-5} M, preferably from about 5×10^{-9} M to about 10^{-7} M.

5 4. In vivo bronchodilator actions of compounds.

4.1 Measurement of bronchodilatation.

Bronchorelaxant activity is measured in in vivo tests in the anaesthetized guinea-pig or rat according to the method described in Underwood et al., Pulm. Pharmacol. 5, 203-212, (1992) in which the effects on bronchospasm induced by histamine (or other spasmogens such as methacholine or leukotriene D₄) is determined. Nebulized aerosols generated from aqueous solutions of compounds of the invention are each administered for one minute to the anaesthetized animals. Alternatively, dry powder formulations made up from compounds of the invention and lactose are blown into the airways of the anaesthetized guinea-pigs or rats by the method described in Underwood et al., J. Pharm. Methods, 26, 203-210, 1991.

4.2 Results.

Compounds within the scope of the invention produce from about 30% up to about 90% decrease in bronchospasm when administered at effective doses of about 4 to about 1000 $\mu\text{g/kg}$, preferably about 4 to about 50 $\mu\text{g/kg}$, without any significant effect on blood pressure.

5. In vivo actions of compounds on antigen (ovalbamin)-induced eosinophilia in guinea-pigs.

5.1 Treatment of animals and measurement of eosinophil numbers.

25 Male Dunkin-Hartley guinea-pigs weighing 200-250 g are sensitized using 10 μg ovalbumin in 1 mL of a 100 mg/mL suspension of aluminium hydroxide, i.p.

Sensitized guinea-pigs are anaesthetised and dry powder formulations of PDE inhibitors or lactose are administered (i.t.) into the airways. In some cases PDE inhibitors are administered orally. 23 hours later the procedure is repeated and 60 minutes later the guinea-pigs are challenged with nebulised saline or ovalbumin (1% in saline) for 15 seconds. 24 hours after challenge the guinea-pigs are killed and the lungs are lavaged with warm saline. Total and differential cell counts are made.

35 5.2 Results.

Compounds within the scope of the invention, administered one hour before challenge, inhibit by at least 50% ovalbumin-induced eosinophilia in

guinea-pigs which is measured 24 hours after challenge, at oral doses of about 1 to about 50 mg/kg, preferably about 1 to 10 mg/kg and inhaled doses of about 4 to 1000 µg/kg, preferably 4 to 50 µg/kg.

6 In Vitro Inhibitory Effects on TNF-α Release by Human Monocytes.

- 5 The effects of compounds on TNF-α production by human peripheral blood monocytes (PBMs) are examined as follows:

6.1. Preparation of blood leukocytes.

- 10 Blood is drawn from normal donors, mixed with dextran, and the erythrocytes allowed to sediment for 35 minutes at 37°C. Leukocytes are fractionated by centrifugation through a discontinuous (18, 20 and 22%) metrizamide gradient. The mononuclear cell fraction comprising 30-40% PBMs is suspended in HBSS and stored at 4°C until use.

6.2. Measurement of TNF-α.

- 15 Cells from the PBM-rich metrizamide fraction are spun down (200 g for 10 minutes at 20°C), resuspended at 10^6 PBMs/mL of medium; RPMI 1640 containing 1%v/v FCS, 50 U/mL penicillin and 50 mg/mL streptomycin (Gibco, U.K.), then plated out in 96 well plates at 2×10^5 cells/ well. The medium (200 µL) is changed to remove any non-adherent cells and the remaining, adherent PBMs left in the incubator overnight (18 hours). One hour prior to
20 challenge, the medium is changed to that containing compound for test or drug vehicle. Control treatments and compounds for test are assayed in quadruplicate wells. Compounds are tested within the concentration range of 3×10^{-10} M to 3×10^{-6} M. Medium (50 µL) with or without 10ng/ml LPS (E. Coli, 055 B5 from Sigma, U.K.) is then added. The incubation is then
25 continued for a further 4 hours. Cell supernatants are removed for storage at -20°C.

- TNF-α levels in cell supernatants are quantified using a standard sandwich ELISA technique. ELISA plates (Costar, U.K.) are coated overnight at 4°C with 3 mg/mL polyclonal goat anti-human TNF-α antibody (British
30 Biotechnology, U.K.) in pH 9.9 bicarbonate buffer. Rabbit polyclonal anti-human TNF-α antiserum (Janssen Biochimica, Belgium) at 1/500 dilution is used as the second antibody and polyclonal goat anti-rabbit IgG horseradish peroxidase (Calbiochem, U.S.A.) at 1/8000 dilution is used as the detection antibody. Color development is measured by absorbance at 450 nm using a
35 Titertek plate reader.

 TNF-α levels are calculated by interpolation from a standard curve using recombinant human TNF-α (British Biotechnology U.K.)(0.125-8 ng/mL).

Data (log-conc. vs. log-resp) are fitted by linear regression ($p > 0.99$) using a Multicalc (Wallac Pharmacia, U.K.) software program. Basal TNF- α levels are less than 100 pg/mL whilst LPS stimulation of the PBMs increases TNF- α levels to 3-10 ng/mL.

5 6.3 Results.

Compounds within the scope of the invention produce 50% inhibition of LPS-induced TNF- α release from human PBMs at concentrations within the range of about 10^{-9} M to about 10^{-6} M., preferably about 10^{-9} M to about 10^{-8} M.

10 7. Inhibitory effects of compounds on antigen-induced bronchoconstriction in the conscious guinea-pig.

7.1. Sensitisation of guinea-pigs and measurement of antigen - induced bronchoconstriction.

Male, Dunkin-Hartley guinea-pigs (550-700 g) are sensitized as above.

15 Specific airways resistance (S_{Raw}) is measured in conscious animals by whole body plethysmography using a variation of the method of Pennock et al., (*J. Appl. Physiol.*, **46**, 399, 1979). Test compounds or vehicle (lactose carrier) are instilled into the airways as dry powders through a metal gavage needle. 30 minutes later, the animals are injected with mepyramine (30 mg/kg i.p.) to
20 prevent anaphylactic collapse and placed into the plethysmography chambers where S_{Raw} is determined at 1 minute intervals. Resting S_{Raw} is then determined. Animals are challenged with an aerosol of ovalbumin and S_{Raw} is determined every 5 minutes for 15 minutes.

7.2. Results.

25 Compounds within the scope of the invention inhibit antigen-induced bronchoconstriction by up to 80% at doses of between about 1 to about 1000 μ g/kg (i.t.), preferably about 1 to about 20 μ g/kg (i.t.).

8. Inhibitory effects of compounds on serum TNF- α levels in LPS - challenged mice.

30 8.1. Treatment of animals and measurement of murine TNF- α .

Female Balb/c mice (age 6-8 weeks, weight 20-22 g from Charles River, U.K.) in groups of five or more animals are dosed p.o. with compounds suspended in 1.5% (w/v) carboxymethyl cellulose then challenged after a minimum period of 30 min with 30 mg of LPS i.p. After 90 min the animals are
35 killed by CO₂ asphyxiation and bled by cardiac puncture. Blood is allowed to clot at 4°C, centrifuged (12,000 g for 5 minutes) and serum taken for TNF- α analysis.

TNF- α levels are measured using a commercially available murine TNF- α ELISA kit, purchased from Genzyme (Cat. no. 1509.00), as recommended by the manufacturer. Values for TNF- α are calculated from a recombinant murine TNF- α standard curve.

5. 8.2. Results.

Compounds within the scope of the invention inhibit LPS-induced serum TNF- α at doses between about 10 and about 10,000 mg/kg, preferably about 10 to about 250 μ g/kg.

The value of the compounds of the invention is enhanced by their very low mammalian toxicity levels.

The following Composition Examples illustrate pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE 1

(\pm)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (1 g) (mean particle size 3.5 microns) and lactose (99 g) (mean particle size 72 microns) were blended together for 30 minutes in a mechanical shaker/mixer. The resulting blend was filled, to a fill weight of 25 mg, into No. 3 hard gelatin capsules, to give a product suitable for use, for example, with a dry powder inhaler.

2.0 COMPOSITION EXAMPLE 2

(\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide (1 g) (mean particle size 3.5 microns) and lactose (99 g) (mean particle size 72 microns) were blended together for 30 minutes in a mechanical shaker/mixer. The resulting blend was filled, to a fill weight of 25 mg, into No. 3 hard gelatin capsules, to give a product suitable for use, for example, with a dry powder inhaler.

COMPOSITION EXAMPLE 3

(\pm)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide (1 g) (mean particle size 3.5 microns) and lactose (99 g) (mean particle size 72 microns) are blended together for 30 minutes in a mechanical shaker/mixer. The resulting blend is filled, to a fill weight of 25 mg, into No. 3 hard gelatin capsules, to give a product suitable for use, for example, with a dry powder inhaler.

COMPOSITION EXAMPLE 4

3.5 (\pm)-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide (1 g) (mean particle size 3.5 microns) and lactose (99 g) (mean particle size 72 microns) are blended together for 30 minutes in a

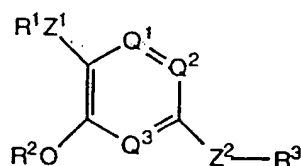
mechanical shaker/mixer. The resulting blend is filled, to a fill weight of 25 mg, into No. 3 hard gelatin capsules, to give a product suitable for use, for example, with a dry powder inhaler.

5 The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED IS:

1. A compound of formula I

5



wherein

10

R¹ is an optionally substituted lower alkyl group;

R² is an optionally substituted oxaaliphatic group;

15

R³ is an optionally substituted aryl group or an optionally substituted heteroaryl group;

Q¹, Q² and Q³ are independently nitrogen, CX or CH;

Z¹ is oxygen or sulfur;

20

Z² is -CH=CH-, -C≡C-, -CH₂-CZ-, -CZCH₂-, -CZ-CZ-, -CH₂-NH-, -CH₂-O-, -CH₂-S-, -CX₂-O-, -CZNH-, -NH-CH₂-, -O-CH₂-, -SCH₂-, -SOCH₂-, -SO₂CH₂-, -O-CX₂-, -O-CZ-, -NH-CZ-, -N=N-, -NH-SO₂-, -SO₂-NH-, -CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH- or -NH-CO-NH-; and

25

Z is oxygen or sulfur; and

X is halo;

30

or an N-oxide thereof or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein R² is tetrahydrofuryl or tetrahydropyranyl.

3. The compound according to claim 2 wherein R² is tetrahydro-3-furyl.

4. The compound according to any one of claims 1 to 3 wherein Z¹ is oxygen.
5. The compound according to any one of claims 1 to 4 wherein R¹ is substituted by halo.
6. The compound according to claim 5 wherein R¹ is substituted by one or more halo on a position of R¹ that is attached to Z¹.
7. The compound according to any one of claims 1 to 6 wherein R³ is phenyl substituted on the 2-position or on both the 2- and 6-positions.
8. The compound according to any one of claims 1 to 6 wherein R³ is heteroaryl substituted on one or both of the positions adjacent to the position of R³ that is attached to Z².
9. The compound according to claim 8 wherein R³ is a 3,5-dihalo-pyrid-4-yl or an N-oxide thereof.
10. The compound according to any one of claims 1 to 9 wherein Z² is -CZNH-; and R¹ is lower alkyl optionally substituted by halo.
11. The compound according to any one of claims 1 to 10 wherein Z² is -CZNH-; and R² is tetrahydrofuryl or tetrahydropyranyl.
12. The compound according to any one of claims 1 to 11 wherein Z² is -CZNH-; and R³ is substituted phenyl or substituted pyridyl, each of which is substituted on one or both of the positions adjacent to a position of R³ that is attached to Z².
13. The compound according to any one of claims 1 to 12 wherein Z² is -CZNH-; and Z¹ is oxygen.
14. The compound according to any one of claims 1 to 9 wherein Z² is -CH=CH-, -C≡C-, -CH₂-CZ-, -CZ-CZ-, -CH₂-NH-, -CH₂-O-, -CH₂-S-, -CX₂-O-, -NH-CH₂-, -O-CH₂-, -SCH₂-, -SOCH₂-, -SO₂CH₂-, -O-CX₂-, -O-CZ-, -NH-CZ-,

-N=N-, -NH-SO₂-, -SO₂-NH-, -CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH- or -NH-CO-NH-.

5 15. The compound according to any one of claims 1 to 14 wherein Q¹ and Q² and Q³ all represent CH.

16. The compound according to any one of claims 1 to 14 wherein Q¹ and Q² are independently nitrogen or CX and Q³ is CH.

10 17. The compound according to any one of claims 1 to 14 wherein Q¹ and Q³ each represents CH and Q² is nitrogen or an N-oxide thereof.

18. The compound according to any one of claims 1 to 14 wherein Q¹ and Q³ each represents CH and Q² is CX.

15

19. The compound according to any one of claims 1 to 14, 16 or 18 wherein CX is CF.

20. The compound according to claim 1 which is:

20

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)benzamide;

25

(±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

30

(±)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;

(±)-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;

35

N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

N-(2-chloro-6-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-(2-trifluoromethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-(2,4,6-trichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dibromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-chloro-6-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 N-(2,6-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-phenyl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 N-(3-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(2,6-dimethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-methylthiophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-bromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(2-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-aminosulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(2-benzoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-(2,5-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-(2-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-dimethylaminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 N-(2-acetylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-hydroxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-methylsulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)benzamide;
- N-(2,6-difluorophenyl)-3-(2-ethoxyethoxy)-4-methoxybenzamide; and
- N-(2,6-difluorophenyl)-4-methoxy-3-(2-methoxyethoxy)benzamide;
- 20 N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- N-(4-chloropyrid-3-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-pyrid-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrazin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrimidin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(3-methylpyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrid-3-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(3-chloropyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-pyrid-4-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-(3,5-dimethylisoxazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 3-[2-(2-butoxyethoxy)ethoxy]-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide;
- N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 N-(3,5-dichloropyrid-4-yl)-3-(2-ethoxyethoxy)-4-methoxybenzamide;
- N-(3,5-dimethylpyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-(2,6-dichloro-4-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- N-(2,6-dichloro-4-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 N-(2,3,5-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dichloro-4-ethoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- 30 N-(2,6-dichloro-4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(2,6-dichlorophenyl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;

- N-(2,6-dichlorophenyl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- 5 N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-methoxy-benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-2H-pyran-2-methyloxy)benzamide;
- 10 N-(3-bromo-5-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxyprop-2-oxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(2-isopropoxyethoxy)-4-methoxybenzamide;
- 15 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(3-methoxy-1-butoxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- 20 N-(2,6-dichloro-4-aminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dichloro-4-acetylamino-phenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(2,6-dichloro-4-formylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide;
- 30 sodium salt of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,4,6-trifluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
- 35 N-(2,6-dichloro-4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

- N-(2,6-dichlorophenyl)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;
- 5 N-(4,6-dichloropyrimid-5-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,3,5,6-tetrafluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 10 N-(3,5-dichloro-2,6-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(5-cyano-3-methylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 15 N-(2,6-dichloro-4-carbamoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- N-(3-chloro-2,5,6-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 20 N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(2-ethoxyethoxy)benzamide;
- N-(4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(3-methyl-5-bromoisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dimethylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-difluoropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;

- N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzamide;
- 5 N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzamide;
- 10 N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzamide;
- N-(3,5-dichloropyrid-4-yl)-4-(fluoromethylthio)-3-(tetrahydro-3-furyloxy)benzamide;
- 15 2',6'-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;
- 3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;
- 20 3,5-dichloro-4-(2-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-oxoethyl)pyridine-N-oxide;
- 2-(3-chloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;
- 25 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(4-pyridyl)ethanone;
- 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-phenylethanone;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzamide;
- 30 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(7-oxabicyclo-[2.2.1]hept-5-en-2-oxy)benzamide;
- 35 N-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2,6-dichlorobenzamide;
- N-[4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2,6-difluorobenzamide;

- N-(2,6-dichlorophenyl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-urea;
- 5 N-(3,5-dichloropyrid-4-yl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)urea;
- 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl 2,6-dichlorobenzoate;
- 2,6-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ether;
- 10 N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzylamine;
- trans-2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- 15 trans-2-(2,6-difluorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- 1-[(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(pyrid-4-yl)ethane-1,2-dione;
- 20 trans-2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)diazene;
- 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-c-1-oxo-r-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- 25 trans-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- N-(2-chlorophenyl)-4-methoxy-3-tetrahydro-3-furyloxybenzene-sulfonamide;
- 30 N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-
- 35 [5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide;

- N-(3,5-difluoropyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- 5 N-(3,5-difluoro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- N-(3,5-dichloro-pyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- 10 N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;
- N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide;
- 15 N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[2-(prop-2-yn-1-oxy)ethoxy]-benzamide;
- 20 N-(3,5-dichloro-1-oxido-4-pyridinio)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide;
- 25 N-(3,5-dichloropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;
- N-(3,5-difluoropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(3-methoxybutoxy)-4-(methylthio)benzamide;
- 30 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone;
- 2-(3,5-dichloropyrid-4-yl)-1-[4-(methylthio)-3-(tetrahydro-3-furyloxy)phenyl]ethanone;
- 35 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)-

- phenyl)ethanone;
- 2-(3,5-dichloropyrid-4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)-phenyl)ethanone;
- 5 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone;
- 10 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanone;
- 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;
- 15 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanone;
- 20 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl)ethanone;
- 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-[4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone;
- 25 2-(3,5-dichloro-4-pyridyl)-1-[3-(2-isopropoxyethoxy)-4-methoxyphenyl]ethanone;
- 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone.
- 30 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)phenyl)ethanone;
- 3,5-dichloro-4-(4-methoxy-3-(tetrahydro-3-furyloxy)phenoxy-methyl)pyridine;
- 35 N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;

- N-(3,5-dichloropyrid-4-yl)-6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 5 N-(3,5-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- N-(2,6-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- N-(3,5-difluoropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- 10 N-(3,5-dichloropyrid-4-yl)-5-methoxy-6-(tetrahydro-3-furyloxy)pyridine-2-carboxamide;
- N-(3,5-dimethylisoxazol-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)-nicotinamide;
- 15 2-(3,5-dichloropyrid-4-yl)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- N-(3,5-dichloropyrid-4-yl)-6-(methylthio)-5-(tetrahydro-3-furyloxy)-nicotinamide;
- 20 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- N-(3,5-dichloropyrid-4-yl)-5-(1-methoxyprop-2-oxy)-6-(methylthio)-nicotinamide;
- 25 2-(3,5-dichloropyrid-4-yl)-1-[5-(1-methoxyprop-2-oxy)-6-(methylthio)pyrid-3-yl]ethanone;
- 30 (S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 35 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide;

(±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

- 5 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

(±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

10

(±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

- 15 (±)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

(±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone; or

- 20 (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone.

21. The compound of claim 20 which is:

- 25 (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)-benzamide;

- 30 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;

(±)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)-benzamide;

35

(±)-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;

- (S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 5 (R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide;
- 10 (±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 15 (±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 20 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (±)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 25 (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone;
- (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone;
- 30 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxyprop-2-oxy)benzamide;
- 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanone; or
- 35

2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone.

22. The compound of claim 21 which is (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide.

23. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

1 0

24. A method for treating a disease state capable of being modulated by inhibiting TNF comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

1 5 25. The method of claim 24 wherein the disease state is an inflammatory disease or autoimmune disease.

2 0 26. The method of claim 24 wherein the disease state is selected from the group consisting of joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias, HIV, AIDS, cachexia, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, 2 5 psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia.

27. The method of claim 26 wherein the disease state is joint-inflammation.

3 0 28. A method for treating a disease state capable of being modulated by inhibiting production of cyclic AMP phosphodiesterase comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

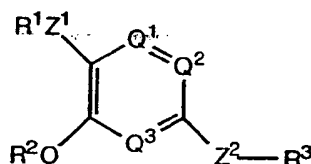
3 5 29. The method of claim 28 wherein the disease state is a pathological condition associated with a function of cyclic AMP phosphodiesterase, eosinophil accumulation or a function of the eosinophil.

30. The method of claim 29 wherein the pathological condition is asthma, atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatic arthritis, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome,
- 5 diabetes insipidus, keratosis, dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, cardiac arrest, stroke and intermittent claudication.
31. The method of claim 30 wherein the pathological condition is asthma.
- 10 32. A process for preparing the compound of claim 1 substantially as hereinbefore described.
33. A compound of claim 1 with reference to the Examples.

AMENDED CLAIMS

[received by the International Bureau on 3 July 1995 (03.07.95);
original claim 1 amended; remaining claims unchanged (17 pages)]

1. A compound of formula I



wherein

R¹ is an optionally substituted lower alkyl group;

R² is an optionally substituted oxaaliphatic group;

R³ is an optionally substituted aryl group or an optionally substituted heteroaryl group;

Q¹, Q² and Q³ are independently nitrogen, CX or CH;

Z¹ is oxygen or sulfur;

Z² is -CH=CH-, -C≡C-, -CH₂-CZ-, -CZCH₂-, -CZ-CZ-, -CH₂-NH-,
-CH₂-O-, -CH₂-S-, -CX₂-O-, -CZNH-, -NH-CH₂-, -O-CH₂-, -SCH₂-, -SOCH₂-,
-SO₂CH₂-, -O-CX₂-, -O-CZ-, -NH-CZ-, -N=N-, -NH-SO₂-, -SO₂-NH-,
-CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH- or -NH-CO-NH-; and

Z is oxygen or sulfur; and

X is halo;

or an N-oxide thereof or a pharmaceutically acceptable salt thereof;

with the proviso that when Z¹ is oxygen, R² is a straight or branched chain oxaaliphatic group, Q¹, Q² and Q³ are CH and Z² is -CH₂-NH- then R³ cannot represent a substituted 3(2H)-pyridazinon-5-yl group.

2. The compound according to claim 1 wherein R² is tetrahydrofuryl or tetrahydropyranyl.
3. The compound according to claim 2 wherein R² is tetrahydro-3-furyl.
4. The compound according to any one of claims 1 to 3 wherein Z¹ is oxygen.
5. The compound according to any one of claims 1 to 4 wherein R¹ is substituted by halo.
6. The compound according to claim 5 wherein R¹ is substituted by one or more halo on a position of R¹ that is attached to Z¹.
7. The compound according to any one of claims 1 to 6 wherein R³ is phenyl substituted on the 2-position or on both the 2- and 6-positions.
8. The compound according to any one of claims 1 to 6 wherein R³ is heteroaryl substituted on one or both of the positions adjacent to the position of R³ that is attached to Z².
9. The compound according to claim 8 wherein R³ is a 3,5-dihalo-pyrid-4-yl or an N-oxide thereof.
10. The compound according to any one of claims 1 to 9 wherein Z² is -CZNH-; and R¹ is lower alkyl optionally substituted by halo.
11. The compound according to any one of claims 1 to 10 wherein Z² is -CZNH-; and R² is tetrahydrofuryl or tetrahydropyranyl.
12. The compound according to any one of claims 1 to 11 wherein Z² is -CZNH-; and R³ is substituted phenyl or substituted pyridyl, each of which is substituted on one or both of the positions adjacent to a position of R³ that is attached to Z².
13. The compound according to any one of claims 1 to 12 wherein Z² is -CZNH-; and Z¹ is oxygen.

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14. The compound according to any one of claims 1 to 9 wherein Z^2 is
 $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{CH}_2-\text{CZ}-$, $-\text{CZ}-\text{CZ}-$, $-\text{CH}_2-\text{NH}-$, $-\text{CH}_2-\text{O}-$, $-\text{CH}_2-\text{S}-$, $-\text{CX}_2-\text{O}-$,
 $-\text{NH}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-$, $-\text{SCH}_2-$, $-\text{SOCH}_2-$, $-\text{SO}_2\text{CH}_2-$, $-\text{O}-\text{CX}_2-$, $-\text{O}-\text{CZ}-$, $-\text{NH}-\text{CZ}-$,
 5. $-\text{N}=\text{N}-$, $-\text{NH}-\text{SO}_2-$, $-\text{SO}_2-\text{NH}-$, $-\text{CZ}-\text{CZ}-\text{NH}-$, $-\text{NH}-\text{CO}-\text{O}-$, $-\text{O}-\text{CO}-\text{NH}-$ or $-\text{NH}-\text{CO}-\text{NH}-$.
15. The compound according to any one of claims 1 to 14 wherein Q^1 and Q^2 and Q^3 all represent CH.
- 10 16. The compound according to any one of claims 1 to 14 wherein Q^1 and Q^2 are independently nitrogen or CX and Q^3 is CH.
17. The compound according to any one of claims 1 to 14 wherein Q^1 and
 15 Q^3 each represents CH and Q^2 is nitrogen or an N-oxide thereof.
18. The compound according to any one of claims 1 to 14 wherein Q^1 and Q^3 each represents CH and Q^2 is CX.
- 20 19. The compound according to any one of claims 1 to 14, 16 or 18 wherein CX is CF.
20. The compound according to claim 1 which is:
- 25 $(\pm)\text{-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide}$;
 $(\pm)\text{-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)benzamide}$;
- 30 $(\pm)\text{-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide}$;
- $(\pm)\text{-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide}$;
- 35 $(\pm)\text{-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide}$;

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- N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-(2-chloro-6-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-trifluoromethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,4,6-trichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 N-(2,6-dibromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-chloro-6-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-(2,6-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-fluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-phenyl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 20 N-(2-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dimethylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(2-methylthiophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-bromophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(2-aminosulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

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- N-(2-benzoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-(2,5-dichlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3-methylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 N-(2-dimethylaminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-acetylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-(2-hydroxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2-methylsulfonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-difluorophenyl)-4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)benzamide;
- 20 N-(2,6-difluorophenyl)-3-(2-ethoxyethoxy)-4-methoxybenzamide; and
- N-(2,6-difluorophenyl)-4-methoxy-3-(2-methoxyethoxy)benzamide;
- 25 N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- N-(4-chloropyrid-3-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrid-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-pyrazin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrimidin-2-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(3-methylpyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-pyrid-3-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

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- N-(3-chloropyrid-2-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 5 N-pyrid-4-yl-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dimethylisoxazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 10 3-[2-(2-butoxyethoxy)ethoxy]-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide;
- N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(2-ethoxyethoxy)-4-methoxybenzamide;
- 15 N-(3,5-dimethylpyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dichloro-4-cyanophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 20 N-(2,6-dichloro-4-methoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,3,5-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(2,6-dichloro-4-ethoxycarbonylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- 30 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- 35 N-(2,6-dichloro-4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

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- N-(2,6-dichlorophenyl)-4-methoxy-3-[(exo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- 5 N-(2,6-dichlorophenyl)-4-methoxy-3-[(endo)-2-oxabicyclo[2.2.1]heptan-6-oxy]benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-methoxy-benzamide;
- 10 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-2H-pyran-2-methyloxy)benzamide;
- N-(3-bromo-5-chloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 15 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxyprop-2-oxy)benzamide;
- N-(3,5-dichloropyrid-4-yl)-3-(2-isopropoxyethoxy)-4-methoxybenzamide;
- N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(3-methoxy-1-butoxy)benzamide;
- 20 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)(thiobenzamide);
- N-(2,6-dichloro-4-aminophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 25 N-(2,6-dichloro-4-acetylamino-phenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,6-dichloro-4-formylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(2,6-dichloro-4-hydroxymethylphenyl)-3-cyclopentyloxy-4-methoxybenzamide;
- 35 sodium salt of N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

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- N-(2,4,6-trifluorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide; and
- N-(2,6-dichloro-4-methoxyphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
5. N-(2,6-dichlorophenyl)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;
- 10 N-(4,6-dichloropyrimid-5-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(2,3,5,6-tetrafluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 15 N-(3,5-dichloro-2,6-difluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(5-cyano-3-methylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 20 N-(2,6-dichloro-4-carbamoylphenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- N-(3-chloro-2,5,6-trifluoropyrid-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 25 N-(3,5-dibromopyrid-4-yl)-4-methoxy-3-(2-ethoxyethoxy)benzamide;
- N-(4-nitrophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 30 N-(3-methyl-5-bromoisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-dimethylisothiazol-4-yl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;
- 35 N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;
- N-(3,5-difluoropyrid-4-yl)-4-(methylthio)-3-(tetrahydro-3-furyloxy)benzamide;

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N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;

5. N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(exo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzamide;

N-(3,5-dichloropyrid-4-yl)-4-(methylthio)-3-[(endo)-2-oxabicyclo[2.2.1]-heptan-6-oxy]benzamide;

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N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-2-methoxy)-4-methoxybenzamide;

- 15 N-(3,5-dichloropyrid-4-yl)-3-(3,4-dihydro-2H-pyran-6-methoxy)-4-methoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-4-(fluoromethylthio)-3-(tetrahydro-3-furyloxy)benzamide;

- 20 2',6'-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;

3,5-dichloropyrid-4-ylmethyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ketone;

- 25 3,5-dichloro-4-(2-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-oxoethyl)pyridine-N-oxide;

2-(3-chloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;

- 30 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(4-pyridyl)ethanone;

1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-phenylethanone;

- 35 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(4-methoxy-3-methylbut-1-en-3-oxy)benzamide;

N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)benzamide;

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- N-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2,6-dichlorobenzamide;
- 5 N-[4-methoxy-3-(tetrahydro-3-furyloxy)phenyl]-2,6-difluorobenzamide;
- N-(2,6-dichlorophenyl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-urea;
- N-(3,5-dichloropyrid-4-yl)-N'-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)urea;
- 10 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl 2,6-dichlorobenzoate;
- 2,6-dichlorobenzyl 4-methoxy-3-(tetrahydro-3-furyloxy)phenyl ether;
- N-(2-chlorophenyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzylamine;
- 15 trans-2-(2,6-dichlorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- trans-2-(2,6-difluorophenyl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)ethene;
- 20 1-[(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(pyrid-4-yl)ethane-1,2-dione;
- trans-2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)diazene;
- 25 1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-c-1-oxo-r-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- 30 trans-1-(4-methoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloro-1-oxopyrid-4-yl)diazene;
- N-(2-chlorophenyl)-4-methoxy-3-tetrahydro-3-furyloxybenzene-sulfonamide;
- 35 N-(3,5-dichloropyrid-4-yl)-3-(tetrahydro-3-furyloxy)-4-trifluoromethoxybenzamide;

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N-(3,5-dichloropyrid-4-yl)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide;

5. N-(3,5-difluoropyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;

N-(3,5-difluoro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;

1 0 N-(3,5-dichloro-pyrid-4-yl)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;

N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)benzamide;

1 5 N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide;

2 0 N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(7-oxa-bicyclo[2.2.1]heptan-2-oxy)benzamide;

N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-[2-(prop-2-yn-1-oxy)ethoxy]-benzamide;

2 5 N-(3,5-dichloro-1-oxido-4-pyridinio)-3-(4,4-dimethyl-3,5,10-trioxatricyclo-[5.2.1.0^{2,6}]decan-8-oxy)-4-methoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;

3 0 N-(3,5-difluoropyrid-4-yl)-3-(1-methoxyprop-2-oxy)-4-(methylthio)-benzamide;

N-(3,5-dichloropyrid-4-yl)-3-(3-methoxybutoxy)-4-(methylthio)benzamide;

3 5 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone;

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- 2-(3,5-dichloropyrid-4-yl)-1-[4-(methylthio)-3-(tetrahydro-3-furyloxy)phenyl]ethanone;
- 5 2-(3,5-dichloropyrid-4-yl)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)-phenyl)ethanone;
- 2-(3,5-dichloropyrid-4-yl)-1-(4-methylthio-3-(tetrahydro-4H-pyran-4-yloxy)-phenyl)ethanone;
- 10 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-methoxy-3-(tetrahydro-4H-pyran-4-yloxy)phenyl)ethanone;
- 1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanone;
- 15 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone;
- 2-(3,5-dichloropyrid-4-yl)-1-[4-methoxy-3-(7-oxabicyclo[2.2.1]hept-5-en-2-oxy)phenyl]ethanone;
- 20 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]-heptan-2-oxy)phenyl)ethanone;
- 25 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-[4-difluoromethoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)phenyl]ethanone;
- 2-(3,5-dichloro-4-pyridyl)-1-[3-(2-isopropoxyethoxy)-4-methoxyphenyl]-ethanone;
- 30 2-(3,5-dichloro-4-pyridyl)-1-(4-difluoromethoxy-3-(1-methoxyprop-2-oxy)phenyl)ethanone.
- 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(1-methoxy-prop-2-oxy)phenyl)ethanone;
- 35 3,5-dichloro-4-(4-methoxy-3-(tetrahydro-3-furyloxy)phenoxy-methyl)pyridine;

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- N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(7-oxabicyclo[2.2.1]heptan-2-oxy)benzamide;
- 5 N-(3,5-dichloropyrid-4-yl)-6-fluoro-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- N-(3,5-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- 10 N-(2,6-dichloropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- N-(3,5-difluoropyrid-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)nicotinamide;
- 15 N-(3,5-dichloropyrid-4-yl)-5-methoxy-6-(tetrahydro-3-furyloxy)pyridine-2-carboxamide;
- N-(3,5-dimethylisoxazol-4-yl)-6-methoxy-5-(tetrahydro-3-furyloxy)-nicotinamide;
- 20 2-(3,5-dichloropyrid-4-yl)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- N-(3,5-dichloropyrid-4-yl)-6-(methylthio)-5-(tetrahydro-3-furyloxy)-nicotinamide;
- 25 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(6-methoxy-5-(tetrahydro-3-furyloxy)pyrid-3-yl)ethanone;
- N-(3,5-dichloropyrid-4-yl)-5-(1-methoxyprop-2-oxy)-6-(methylthio)-nicotinamide;
- 30 2-(3,5-dichloropyrid-4-yl)-1-[5-(1-methoxyprop-2-oxy)-6-(methylthio)pyrid-3-yl]-ethanone;
- (S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
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(R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;

(±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide;

(±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

10 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

(±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

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(±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

20 (±)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;

(±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone; or

25 (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone.

21. The compound of claim 20 which is:

30 (±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)benzamide;

(±)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-4-pyranyloxy)-benzamide;

35 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;

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- (±)-N-(3,5-dichloro-4-pyridyl)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 5 (±)-N-(3,5-dichloro-1-oxido-4-pyridino)-4-difluoromethoxy-3-(tetrahydro-3-furyloxy)benzamide;
- (S)-(+)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- 10 (R)-(-)-N-(3,5-dichloro-4-pyridyl)-4-methoxy-3-(tetrahydro-3-furyloxy)-benzamide;
- (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-methoxyprop-2-yloxy)benzamide;
- 15 (±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 20 (±)-N-(3,5-dichloropyrid-4-yl)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 25 (±)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- (±)-N-(3,5-difluoropyrid-4-yl)-5-methoxy-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide;
- 30 (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloropyrid-4-yl)ethanone;
- (±)-(5-methoxy-4-(tetrahydro-3-furyloxy)pyrid-2-yl)-2-(3,5-dichloro-1-oxido-4-pyridyl)ethanone;
- 35 N-(3,5-dichloropyrid-4-yl)-4-methoxy-3-(1-methoxyprop-2-oxy)benzamide;

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1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)-2-(3,5-dichloropyrid-4-yl)ethanone; or

5 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-(4-difluoromethoxy-3-(tetrahydro-3-furyloxy)phenyl)ethanone.

22. The compound of claim 21 which is (\pm)-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-1-oxido-4-(tetrahydro-3-furyloxy)-2-pyridinecarboxamide.

10

23. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

15 24. A method for treating a disease state capable of being modulated by inhibiting TNF comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

25. The method of claim 24 wherein the disease state is an inflammatory
20 disease or autoimmune disease.

26. The method of claim 24 wherein the disease state is selected from the group consisting of joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, gram negative sepsis, toxic
25 shock syndrome, acute respiratory distress syndrome, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias, HIV, AIDS, cachexia, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic
30 glomerulonephritis, inflammatory bowel disease and leukemia.

27. The method of claim 26 wherein the disease state is joint inflammation.

28. A method for treating a disease state capable of being modulated by
35 inhibiting production of cyclic AMP phosphodiesterase comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

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29. The method of claim 28 wherein the disease state is a pathological condition associated with a function of cyclic AMP phosphodiesterase, eosinophil accumulation or a function of the eosinophil.
- 5
30. The method of claim 29 wherein the pathological condition is asthma, atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatic arthritis, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, dermatitis, cerebral senility, multi-infarct
- 10 dementia, senile dementia, memory impairment associated with Parkinson's disease, cardiac arrest, stroke and intermittent claudication.
31. The method of claim 30 wherein the pathological condition is asthma.
- 15 32. A process for preparing the compound of claim 1 substantially as hereinbefore described.
33. A compound of claim 1 with reference to the Examples.

AMENDED SHEET (ARTICLE 19)

STATEMENT UNDER ARTICLE 19(1) PCT

Claim 1 has been amended by the inclusion of a proviso to clearly distinguish the claimed compounds from compounds disclosed as SRS-A antagonists in EP-A-0186817 cited in the International Search Report. A similar amendment will be required to be made on page 7 of the description during the further prosecution of the application.

INTERNATIONAL SEARCH REPORT

Intern al Application No PCT/GB 95/00157					
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D213/75 C07D307/20 C07D405/14 C07D405/12 C07D413/12 C07D309/12 C07D417/12 C07D307/00 C07C235/56 A61K31/34 A61K31/35 A61K31/44					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D C07C A61K					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
A	WO,A,93 25517 (CELLTECH LIMITED) 23 December 1993 cited in the application see the whole document ---				1-33
A	WO,A,92 12961 (RHONE POULENC RORER LIMITED) 6 August 1992 cited in the application see the whole document ---				1-33
X,P	WO,A,94 02465 (RHONE POULENC RORER LIMITED) 3 February 1994 see the whole document ---				1-33
X	EP,A,0 186 817 (NISSAN CHEMICAL INDUSTRIES, LTD.) 9 July 1986 see compound 148 see claims 1,9 -----				1,4,8, 14,15,23
<div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>					
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>					
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">29 March 1995</div>			Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">- 3. 05. 95</div>		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016			Authorized officer <div style="text-align: center; font-weight: bold;">Bosma, P</div>		

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/GB 95/00157

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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